(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) Publication number: 0 181 779 A1

(12) **EUROPEAN PATENT APPLICATION**

(21) Application number: 85308227.9

(22) Date of filing: 12.11.85

(51) Int. Cl.⁴: C 07 D 285/12
C 07 D 277/16, C 07 D 277/74
C 07 D 239/58, C 07 D 249/12
A 61 K 31/41, A 61 K 31/425
A 61 K 31/505

(30) Priority: 12.11.84 JP 238991/84
01.10.85 JP 219327/85

(43) Date of publication of application:
21.05.86 Bulletin 86/21

(84) Designated Contracting States:
AT BE CH DE FR GB IT LI NL SE

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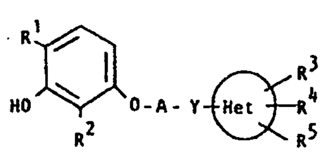
(54) **Heterocyclic compounds, their production, and medicaments containing them.**

(57) Compounds of formula I



(I)

and salts thereof are useful for the treatment and prophylaxis of allergic diseases. Production and use of the compounds is described.

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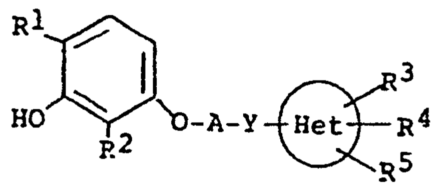
HETEROCYCLIC COMPOUNDS, THEIR PRODUCTION, AND MEDICAMENTS CONTAINING THEM

This invention relates to the medicinally useful compounds of the following general formula (I) and the salts thereof, and to their production :



(I)

wherein R^1 represents a lower acyl group; R^2 represents a lower alkyl group; A represents a lower alkylene group which may be hydroxy-substituted; Y represents an oxygen atom, a sulfur atom, a carbonylimino group (-CONH-), or an iminocarbonyl group (-NHCO-); (Het) represents a 5- or 6-membered heterocyclic ring which has 1 to 3 hetero atoms selected from oxygen sulfur and nitrogen, is bonded directly to Y, and may be fused with a benzene ring; and R^3, R^4 and R^5, each of which may be present or absent, are the same or different and selected from lower alkyl groups, groups of formula $-A^1-R^6$ [wherein A^1 represents a lower alkylene group and R^6 represents a hydroxy group, a mercapto group, a carboxy group, or a (lower alkoxy)carbonyl group], a hydroxy group, a mercapto group, lower alkoxy groups, lower alkylthio groups, groups of formula

$-Y^1-A^2-R^7$ [wherein Y^1 represents an oxygen atom or a sulfur atom, A^2 represents a lower alkylene group, and R^7 represents a carboxy group, a (lower alkoxy)-carbonyl group, a hydroxyaminocarbonyl group, a mono- or a di-(lower alkyl)aminocarbonyl group, or an N-(lower alkyl)hydroxyaminocarbonyl group] an oxo group (=O), a thioxo group (=S), an amino group, groups of formula $-NH-R^8$ [wherein R^8 represents a carboxy lower alkyl group or a (lower alkoxy)carbonyl (lower alkyl) group], groups of formula $-NH-CO-R^9$ [wherein R^9 represents a carboxy(lower alkyl) group, a (lower alkoxy) carbonyl (lower alkyl) group, a (lower alkoxy) phenyl (lower alkoxy) carbonyl (lower alkyl) group, a carboxy group, or a (lower alkoxy)carbonyl group], a carboxy group, or groups of formula $-CO-R^{10}$ [wherein R^{10} represents a lower alkoxy group].

It is generally considered that in allergic asthma and other atopic diseases of man or anaphylactic shock in animals, various chemical mediators are released from the lung and other tissues and cause problems such as the constriction of smooth muscles, e.g., bronchi, pulmonary artery, etc., and the enahncement of vascular permeability in the skin. As such chemical mediators, there are histamine and SRS-A. Histamine plays an important role in guinea pig

anaphylactic shock but not in allergic asthma in man (Eiser, "Pharmacology and Therapeutics", 17, 239-250 (1982)), whereas some evidence suggests that SRS-A is the most important chemical mediator of allergic asthma in man (Brocklehurst, "Journal of Physiology", 151, 416-435(1960); Austen and Orange, "American Review of Respiratory Diseases", 12, 423-436(1975); Adams and Lichtenstein, "Journal of Immunology", 122, 555-562(1979)).

The development of medicaments for prophylaxis, elimination and reduction of immediate hypersensitivity reactions has aimed at inhibiting the production and release of such chemical mediators or antagonizing the action of these chamical mediators. As an inhibitor of histamine release, disodium cromoglycate is well known and as an inhibitor of actions induced by histamine, various anti-histaminics are commercially available. SRS-A is known as a slowly reactive and long acting chemical mediator while histamine is a rapid acting and short acting chemical mediator, and it has recently been recognized that SRS-A is a mixture of Leukotriens C_4, D_4 and E_4 the structure of which have been clarified by Dr. Samuelsson. SRS-A, i.e., Leukotriens are lipoxigenase products of polyunsaturated fatty acids (in particular, arachidonic acid) and it has been reported that SRS-A has various activities such as enhancment of mucus production, reduction of mucociliary transport, coronary artery constrictor action, reduction of cardiac contractibility,

etc., besides the aforesaid action as chemical mediator in immediate hypersensitivity reactions.

To delineate the dynamic roles of SRS-A and to modulate its actions in various pathological conditions, obviously it would be highly desirable to have a specific and in vivo active receptor antagonist. Furthermore, it is clinically desirable to prepare an orally active compound. FPL 55712* of Fisons shows potent anti-SRS-A activity in isolated tissues (Augstein et al, Nature New Biol., 245, 215-217(1973)). However, its biological half life is very short and its absorption by the oral route is very poor (Sheard et al, Mongr. Allergy, 12, 245-249(1977)).

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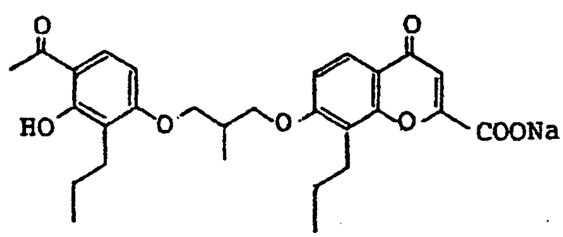
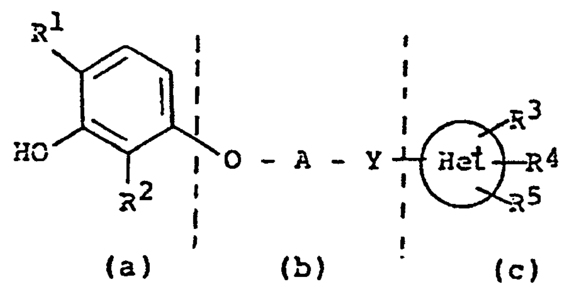


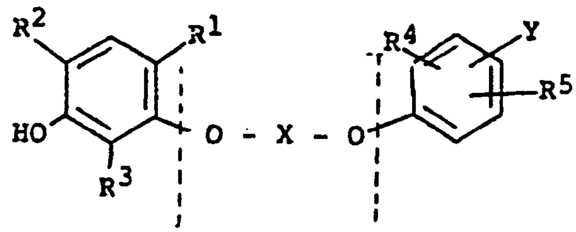
We have found that

the compounds shown by general formula (I) described above and the salts thereof strongly antagonize the actions of SES-A, are effective in oral administration, and show very weak toxicity.

The compounds of this invention have the structural characteristic that the 5- or 6-membered heterocyclic ring (c) having 1 to 3 hetero atoms is directly bonded to moiety (b) :



Related known compounds are e.g. above-described FPL 55712 of Fisons, and those of UK Patent No.2,058,785 which have the general formula



(a) (b) (c)

In these compounds, moiety (c) is a banzene ring or a benzene ring with which a heterocyclic ring is condensed and in each case the benzene ring is directly bonded to moiety (b). The only known instance of such compounds wherein the moiety (c) is a heterocyclic ring is that where it is a tetrazole (Japanese Patent Publication No.164,344/84).

The term "lower" in this specification means a straight or branched carbon chain of 1 to 6 carbon atoms.

Accordingly, the lower alkyl groups herein include a methyl group, an ethyl group, a propyl group, an isopropyl group, a butyl group, an isobutyl group, a sec-butyl group, a tert-butyl group, a pentyl group, an isopentyl group, a neopentyl group, a tert-pentyl group, a 1-methylbutyl group, a 2-methylbutyl group, a 1,2-dimethylpropyl group, a hexyl group, an isohexyl group, a 1-methylpentyl group, a 2-methylpentyl group, a 3-methylpentyl group, a 1,1-dimethylbutyl group, a 1,2-dimethylbutyl group, a 2,2-dimethylbutyl group, a 1,3-dimethylbutyl group, a 2,3-dimethylbutyl group,

a 3,3-dimethylbutyl group, a 1-ethylbutyl group, a 2-ethylbutyl group, a 1,1,2-trimethylpropyl group, a 1,2,2-trimethylpropyl group, a 1-ethyl-1-methylpropyl group, a 1-ethyl-2-methylpropyl group, etc.

Also, the lower acyl groups include a formyl group, an acetyl group, a propionyl group, a butyryl group, an isobutyryl group, a valeryl group, an iso-valeryl group, a pivaloyl group, a hexanoyl group, etc.

Furthermore, the lower alkylene groups include straight chain and branched alkylene groups having 1 to 6 carbon atoms, such as a methylene group, an ethylene group, a methylmethylene group ($-\overset{CH_3}{\overset{|}{C}H}-$), a trimethylene group, a 1-methylethylene group ($-\overset{CH_3}{\overset{|}{C}H}CH_2-$), a 2-methylethylene group ($-CH_2\overset{CH_3}{\overset{|}{C}H}-$), a tetramethylene group, a 1-methyltrimethylene group, a 2-methyltrimethylene group, a 3-methyltrimethylene group, a 1-ethylethylene group, a 2-ethylethylene group, a pentamethylene group, a 1-methyltetramethylene group, a 2-methyltetramethylene group, a 3-methyltetramethylene group, a 4-methyltetramethylene group, a hexamethylene group, etc. Practical examples of the hydroxy-substituted lower alkylene groups are those in which a hydrogen atom at an optional position of an above-described lower alkylene group is substituted by a hydroxy group, such as a hydroxy-methylene group, a 1-hydroxyethylene group, a 2-hydroxy-

ethylene group, a 1-hydroxytrimethylene group, a 2-hydroxytrimethylene group, a 3-hydroxytrimethylene group, a 1-hydroxy-2-methylethylene group, a 2-hydroxy-1-methylethylene group, a 1-hydroxytetramethylene group, a 2-hydroxytetramethylene group, a 3-hydroxytetramethylene group, a 4-hydroxytetramethylene group, a 2-hydroxy-1-methyltrimethylene group, a 2-hydroxy-3-methyltetramethylene group, a 2-hydroxypentamethylene group, a 4-hydroxypentamethylene group, a 2-hydroxyhexamethylene group, a 5-hydroxyhexamethylene group, etc.

Also, the lower alkoxy groups herein include straight chain and branched alkoxy groups having 1 to 6 carbon atoms, such as a methoxy group, an ethoxy group, a propoxy group, an isopropoxy group, a butoxy group, an isobutoxy group, a sec-butoxy group, a tert-butoxy group, a pentyloxy group, an isopentyloxy group, a neopentyloxy group, a tert-pentyloxy group, a hexyloxy group, etc.

The lower alkylthio groups are straight chain or branched alkylthio groups having 1 to 6 carbon atoms and include a methylthio group, an ethylthio group, a propylthio group, an isopropylthio group, a butylthio group, an isobutylthio group, a sec-butylthio group, a tert-butylthio group, a pentylthio group, an isopentylthio group, a neopentylthio group, a tert-pentylthio group, a hexylthio group, etc.

The lower alkoxycarbonyl groups have

straight or branched chains of 1 to 6 carbon atoms and a carboxy group and include a methoxycarbonyl group, an ethoxycarbonyl group, a propoxycarbonyl group, an isopropoxycarbonyl group, a butoxycarbonyl group, an isobutoxycarbonyl group, a sec-butoxycarbonyl group, a tert-butoxycarbonyl group, a pentyloxycarbonyl group, an isopentyloxycarbonyl group, a neopentyloxycarbonyl group, a tert-pentyloxycarbonyl group, a hexyloxycarbonyl group, etc.

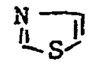
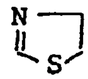
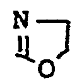
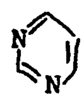
Also, the term "mono- or di-lower alkylaminocarbonyl group" means an aminocarbonyl group with one or two hydrogen atoms substituted by above-described lower alkyl group(s); examples are an aminocarbonyl group mono-substituted by a straight chain or branched alkyl group having 1 to 6 carbon atoms, such as a methylaminocarbonyl group, an ethylaminocarbonyl group, a propylaminocarbonyl group, an isopropylaminocarbonyl group, a butylaminocarbanoyl group, an isobutylaminocarbonyl group, a pentylaminocarbonyl group, an isopentylaminocarbonyl group, a hexylaminocarbonyl group, etc.; an aminocarbonyl group symmetrically di-substituted by a straight chain or branched alkyl group having 1 to 6 carbon atoms, such as a dimethylaminocarbonyl group, a diethylaminocarbonyl group, a dipropylaminocarbonyl group, a diisopropylaminocarbonyl group, a dibutylaminocarbonyl group, a dipentylaminocarbonyl group, a dihexylaminocarbonyl group, etc.;

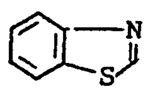
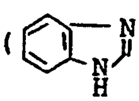
and an aminocarbonyl group asymmetrically disubstituted by different alkyl groups each having 1 to 6 carbon atoms, such as an ethylmethylaminocarbonyl group, a methylpropylaminocarbonyl group, an ethylpropylaminocarbonyl group, a butylmethylaminocarbonyl group, a butylethylaminocarbonyl group, a butylpropylaminocarbonyl group, etc.

The term "N-(lower alkyl)hydroxyaminocarbonyl group" means a hydroxyaminocarbonyl group ($-CON{<}^{H}_{OH}$) in which the hydrogen atom bonded to the nitrogen atom is substituted by an above-described lower alkyl group. Practical examples thereof are an N-methylhydroxyaminocarbonyl group, an N-ethylhydroxyaminocarbonyl group, an N-propylhydroxyaminocarbonyl group, an N-isopropylhydroxyaminocarbonyl group, an N-butylhydroxyaminocarbonyl group, an N-isobutylhydroxyaminocarbonyl group, an N-pentylhydroxycarbonyl group, an N-isopentylhydroxyaminocarbonyl group, an N-hexylhydroxyaminocarbonyl group, etc.

The terms "carboxy lower alkyl group","(lower alkoxy)carbonyl (lower alkyl) group", and "(lower alkoxy)phenyl (lower alkoxy)carbonyl(lower alkyl)group" mean an aforesaid lower alkyl group an optional hydrogen atom of which is substituted by the "carboxy group","(lower alkoxy)carbonyl group" or "(lower alkoxy)phenyl (lower alkoxy)carbonyl group", respectively. In addition, the "(lower alkoxy)phenyl(lower alkoxy)carbonyl group" means an aforesaid "(lower alkoxy)carbonyl group" an optional

hydrogen atom of which is substituted by a phenyl group having an above-described lower alkoxy group at the ortho-, meta- or para-position.

Preferred examples of the 5- or 6-membered heterocyclic ring having 1 to 3 hetero atoms selected from an oxygen atom, a sulfur atom, and a nitrogen atom shown by (Het) are a 1,3-thiazole ring (), a 4,5-dihydro-1,3-thiazole ring (), an isothiazole ring (), a 1,2,3-thiadiazole ring (), a 1,2,4-thiadiazole ring (), a 1,3-oxazole ring (), a 4,5-dihdyroxazole ring (), an isoxazole ring (), a 1,3,4-oxadiazole ring (), an imidazole ring (), a pyrazole ring (), a 1H-1,2,3-triazole ring (), a 1H-1,2,4-triazole ring (), a 2H-pyran ring (), a 4H-pyran ring (), a pyrimidine ring (), etc.

Examples of the condensates of these heterocyclic rings and a benzene ring are a benzothiazole ring (), a benzimidazole ring (), etc.

When the heterocyclic ring is fused with a benzene ring, R^3, R^4, and R^5 above indicate groups bonded directly to the heterocyclic ring - though one, two or all three may be absent just as in the cases where Het is a heterocyclic ring alone. In the case of some fused rings, according to the heterocyclic moiety, at least one R^3, R^4 and R^5 is inevitably absent.

Examples of R^3, R^4, and R^5 on the heterocyclic ring are lower alkyl groups; hydroxy-, mercapto-, carboxy- and (lower alkoxy)carbonyl-substituted lower alkylene groups of formula $-A^1-R^6$; -OH; -SH; lower alkoxy groups; lower alkylthio groups; carboxy-, (lower alkoxy)carbonyl-, mono- or di-(lower alkyl)aminocarbonyl-, hydroxyaminocarbonyl-, and N-(lower alkyl)hydroxyaminocarbonyl-substituted lower alkoxy and lower alkylthio groups of formula $-Y^1-A^2-R^7$; an oxo group; a thioxo group; an amino group; carboxy- and (lower alkoxy)carbonyl-substituted lower alkylamino groups of formula $-NH-R^8$; carboxy (lower alkanoyl)amino groups; (lower alkoxy)carbonyl (lower alkanoyl)amino groups; (lower alkoxy)phenyl (lower alkoxy)carbonyl (lower alkanoyl)amino groups; oxaloamino and (lower alkoxy)oxalyl-amino groups of formula $-NH-CO-R^9$; a carboxy group; and (lower alkoxy)carbonyl groups of formula $-CO-R^{10}$.

The "lower alkanoyl group" of the above-described carboxy (lower alkanoyl)amino, (lower alkoxy)carbonyl (lower alkanoyl)amino, and (lower alkoxy)phenyl (lower alokoxy)carbonyl (lower alkanoyl)amino groups is a

straight chain or branched alkylcarbonyl group having 2 to 6 carbon atoms, such as an acetyl group, a propionyl group, a butyryl group, an isobutyryl group, a valeryl group, an isovaleryl group, a pivaloyl group, a hexanoyl group, etc.

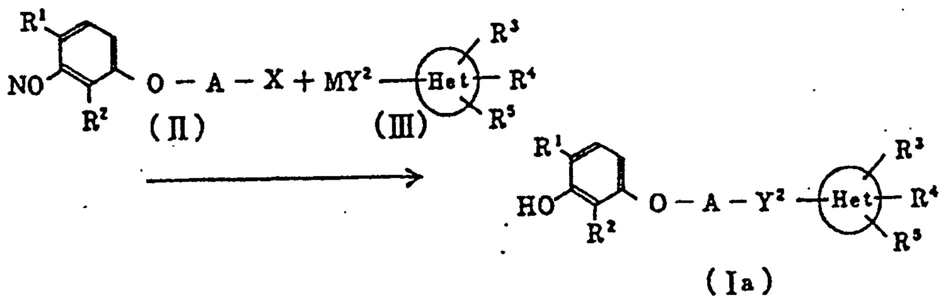
The compounds of this invention include optical isomers based on the existence of asymmetric carbon; tautomers based on the kind of heterocyclic ring or the presence of an oxo group, a hydroxy group, a thioxo group or a mercapto group; and cis-trans geometrical isomers based on two different substituents bonded to the saturated or partially saturated heterocyclic ring. This invention includes all such isomers, individually and in any admixture of two or more thereof.

Some of the compounds of this invention form salts and the invention includes these salts. Examples of such salts are those with inorganic base such as sodium, potassium, etc.; those with organic base such as ethylamine, propylamine, diethylamine, triethylamine, morpholin, piperidine, N-ethylpiperidine, diethanolamine, cyclohexylamine, etc.; those with basic amino acid such as lysine, ornithine, etc.; the ammonium salts; salts with mineral acid such as hydrochloric acid, sulfuric acid, phosphoric

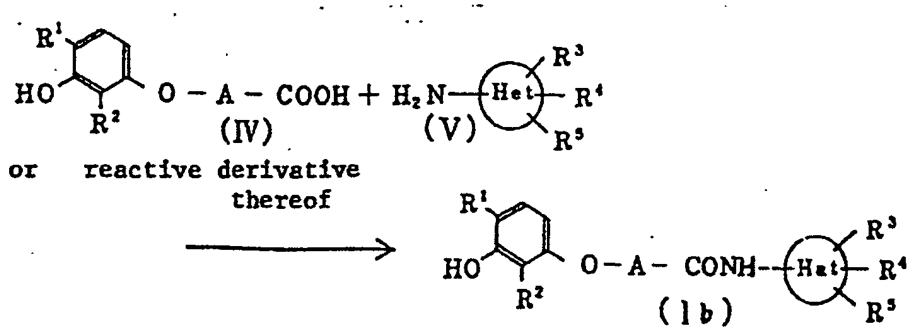
acid, hydrobromic acid, etc.; salts with organic acid such as acetic acid, oxalic acid, succinic acid, citric acid, maleic acid, malic acid, fumaric acid, tartaric acid, methansulfonic acid, etc.; and salts with acidic amino acid such as glutamic acid, aspartic acid, etc.

The compounds of this invention shown by general formula (I) can be prepared by various processes. Typical production process of the compounds are illustrated below :

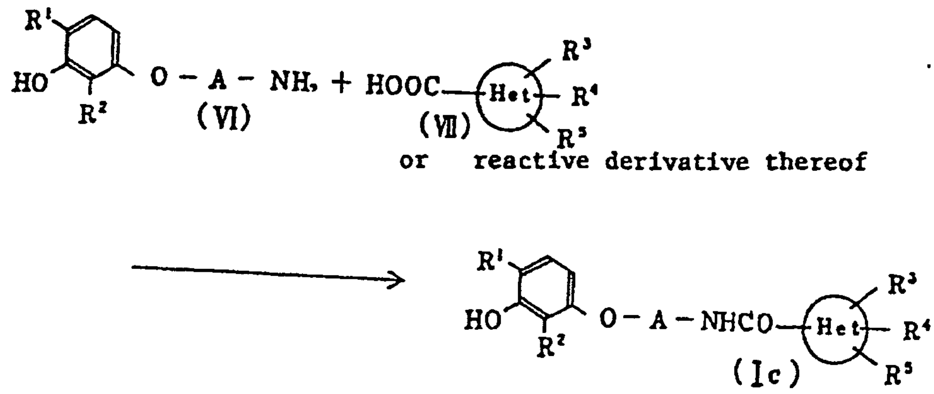
Process A



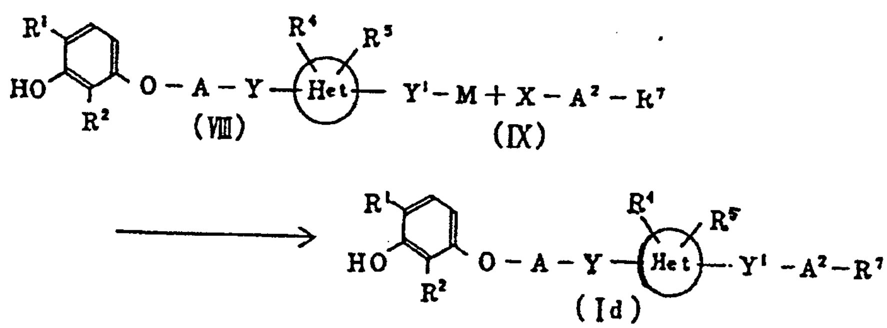
Process B



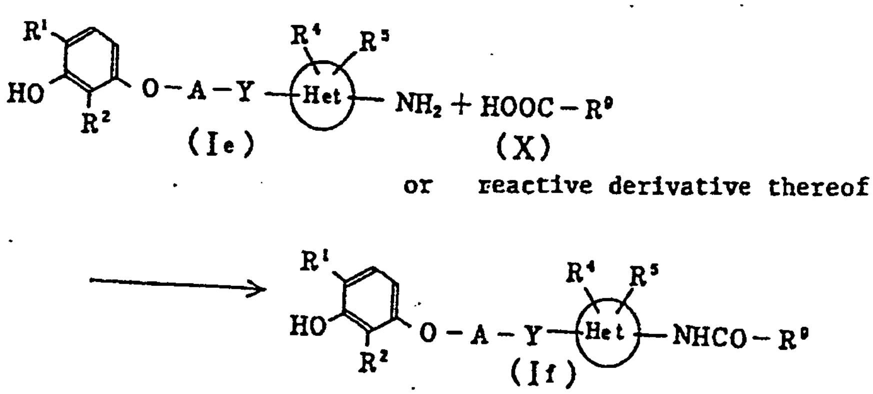
Process C



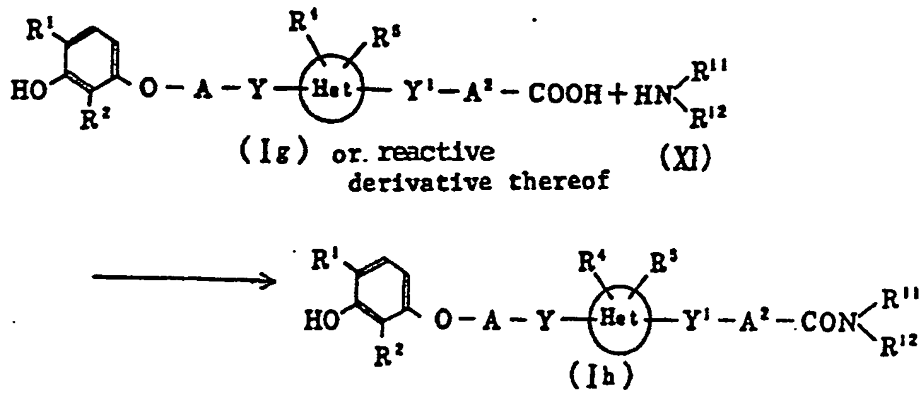
Process D



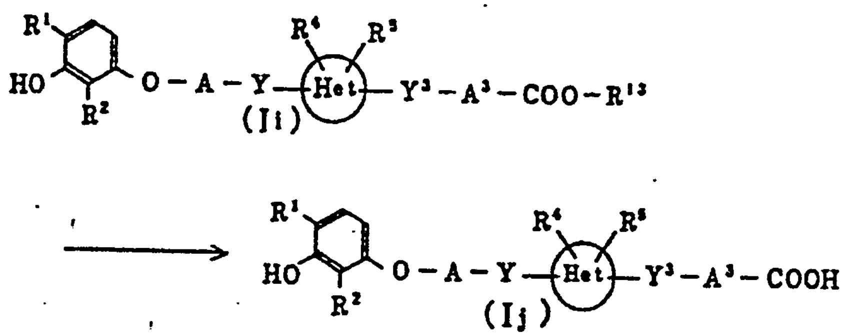
Process E



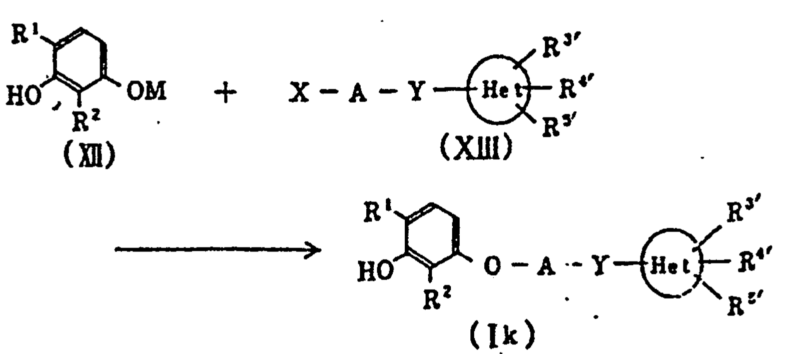
Process F



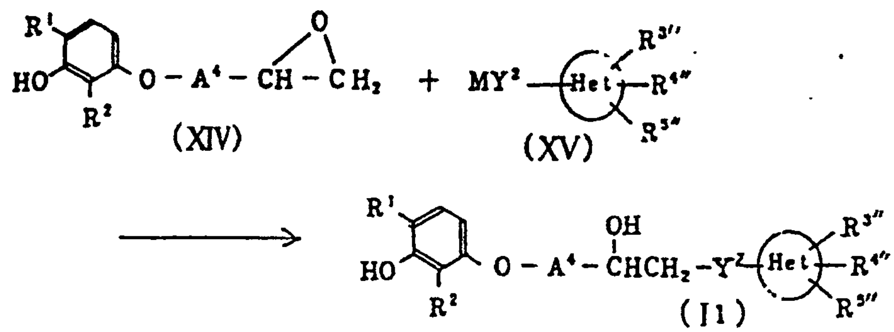
Process G



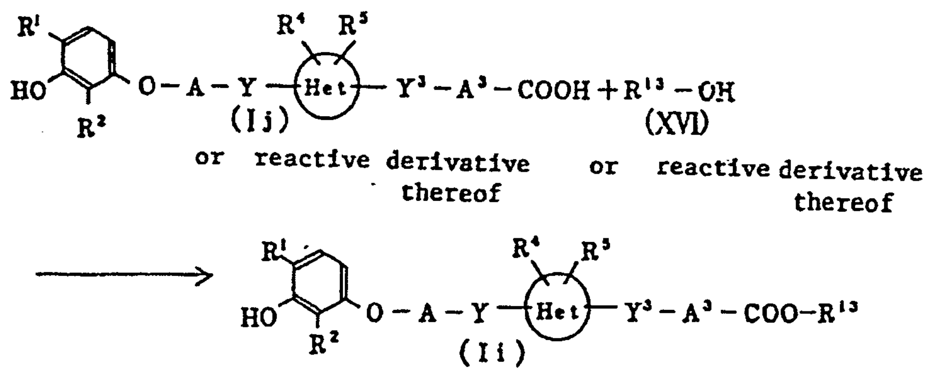
Process H



Process I



Process J



In the above formulae, R^1, R^2, A, Y, Het, R^3, R^4, R^5, Y^1, A^2, R^7, and R^9 have the same significance as defined above and other symbols have the following meanings:

X: A halogen atom.

M: A hydrogen atom or an alkali metal atom.

Y^2: An oxygen atom or a sulfur atom.

R^{11}: A hydrogen atom or a lower alkyl group.

R^{12}: A lower alkyl group or a hydroxy group.

Y^3: A single bond, an oxygen atom, a sulfur atom, or an imino group (-NH-).

R^{13}: A lower alkyl group.

A^3: A single bond, a lower alkylene group or, when

Y^3 is an imino group; a carbonyl group or a carbonyl lower alkylene group.

A^4: A single bond or a lower alkylene group having 1 to 4 carbon atoms.

$R^{3'}$, $R^{4'}$, and $R^{5'}$: each present or absent, the same or different and each may be a lower alkyl group, $-A^1-R^{6'}$ (wherein A^1 is as defined above and $R^{6'}$ is a hydroxy group, a carboxy group, or a (lower alkoxy)carbonyl group), a hydroxy group, a lower alkoxy group, a lower alkylthio group, $-Y^1-A^2-R^{7'}$ (wherein Y^1 and A^2 are as defined above and $R^{7'}$ represents a (lower alkoxy)carbonyl group, a hydroxyaminocarbonyl group, a mono- or di-(lower alkyl)aminocarbonyl group, or an N-(lower alkyl)hydroxyaminocarbonyl group), an oxo group (=O), an amino group, $-NH-R^{8'}$ (wherein $R^{8'}$ represents a (lower alkoxy)carbonyl group), $-NH-CO-R^{9'}$ (wherein $R^{9'}$ represents a (lower alkoxy)carbonyl (lower alkyl) group, a (lower alkoxy)phenyl (lower alkoxy)carbonyl (lower alkyl) group, or a (lower alkoxy)carbonyl group), a carboxy group, or $-CO-R^{10}$ (wherein, R^{10} is as defined above).

$R^{3''}$, $R^{4''}$, and $R^{5''}$: each present or absent, the same or different, and each may be a lower alkyl group, $-A^1-R^{6''}$ (wherein A^1 is as defined

above and $R^{6''}$ represents a hydroxy group, a carboxy group, or a (lower alkoxycarbonyl group), a hydroxy group, a lower alkoxy group, a lower alkylthio group,

$-Y^1-A^2-R^7$ (wherein Y^1, A^2, and R^7 are as defined above), an oxo group (=O), an amino group,
$-NH-R^8$ (wherein R^8 is as defined above),
$-NH-CO-R^9$ (wherein R^9 is as defined above), a carboxy group, or $-CO-R^{10}$ (wherein R^{10} is as defined above).

A halogen atom can be a iodine atom, a bromine atom, a chlorine atom, etc., and an alkali metal atom can be sodium, potassium, etc.

Process A:

A compound of this invention wherein Y is an oxygen atom or a sulfur atom is produced by reacting a halogen compound (II) and a hydroxy compound or mercapto compound (III), or an alkali metal substitution product thereof.

The reaction can be performed using the compounds (II) and (III in almost equimolar amounts, or with a slight excess of one, in an organic solvent such as dimethylformamide, dimethylsulphoxide, methanol, ethanol,

propanol, acetone, methyl ethyl ketone, tetrahydrofuran, chloroform, dioxane, etc., water, or a mixed solvent thereof.

When a hydroxy- or mercapto-substituted heterocyclic compound is used as the compound (III), reaction is usually in the presence of base and suitable examples of such a base are potassium carbonate, Triton B, potassium hydroxide, sodium hydroxide, sodium hydride, etc.

There is no particular restriction on the reaction temperature but the reaction is usually performed at room temperature or under heating.

Process B:

A compound (Ib) which is a compound (I) of this invention wherein Y is a carbonylimino group (-CONH-) is produced by reacting carboxylic acid (IV) or reactive derivative thereof and amino compound (V).

As reactive derivatives of compound (IV), there are acid halides such as acid chloride, acid bromide, etc.; acid azides, active esters prepared with N-hydroxybenzotriazole or N-hydroxysuccinimide; symmetric acid anhydrides; mixed acid anhydrides prepared with alkyl chlorocarbonate or p-toluenesulfonyl chloride; etc.

When compound (IV) is used as a free carboxylic acid, it is advantageous to perform the reaction in the presence of a condensing agent such

as dicyclohexylcarbodiimide, 1,1'-carbonyldiimidazole, etc.

The reaction can be performed using the compound (IV) or reactive derivative thereof and compound (V) in almost equimolar amounts, or with slight excess of one, in an organic solvent inactive to the reaction, such as pyridine, tetrahydrofuran, dioxane, ether, benzene, toluene, xylene, methylene chloride, dichloroethane, chloroform, dimethylformamide, ethyl acetate, acetonitrile, etc.

According to the kind of the reactive derivative, it is sometimes advantageous for smooth reaction to add a base such as triethylamine, pyridine, picoline, lutidine, N,N-dimethylaniline, potassium carbonate, sodium hydroxide, etc. Pyridine can be also used as the solvent.

The reaction temperature depends upon the kind of reactive derivative and is not critical.

Process C:

A compound (Ic), which is a compound (I) of this invention (I) wherein Y is an iminocarbonyl group (-NHCO-) is produced by reacting amine (VI) and carboxylic acid (VII).

The reaction conditions, etc., are as in Process B.

Process D:

A compound (Id) wherein the heterocyclic ring is substituted by a lower alkoxy group, a lower alkylthio group, a (lower alkoxy)carbonyl lower alkoxy group, a lower(alkoxy)carbonyl lower alkylthio group, a carboxy lower alkoxy group, a carboxy lower alkylthio group, a (lower alkoxy)carbonyl lower alkoxy group, or a (lower alkoxy)carbonyl lower alkylthio group can be produced by reacting compound VIII of this invention wherein the heterocyclic ring is substituted by a hydroxy group or a mercapto group, or alkali metal substitution product thereof, and halogen compound (IX).

The reaction can be performed almost as in Process A. When a compound (VIII) whose heterocyclic ring has a plurality of $-Y^1-M$ substituents is used as raw material, it is possible to prepare a product having a corresponding number of $-Y^1-A^2-R^7$ substituents.

Process E:

A compound of this invention wherein the heterocyclic ring is substituted by a carboxy lower alkanoylamino group, a (lower alkoxy)carbonyl lower alkanoylamino group, a (lower alkoxy)phenyl (lower alkoxy)carbonyl lower alkanoylamino group, an oxaloamino group or a (lower alkoxy)oxalylamino group can be produced by reacting

compound (Ie), wherein the heterocyclic ring is substituted by an amino group, with carboxylic acid (X) or reactive derivative thereof.

The reaction conditions, etc., are almost as in Processes B and C.

When a compound whose heterocyclic ring has plural amino groups is used as the raw material, a product wherein all the amino groups are reacted can be obtained.

Process F:

A compound of this invention wherein the heterocyclic ring is substituted by a mono- or di-(lower alkyl)aminocarbonyl lower alkoxy group, a mono- or di-(lower alkyl)aminocarbonyl lower alkylthio group, an (N-lower alkyl)hydroxyaminocarbonyl lower alkoxy group, or an (N-lower alkyl)hydroxyaminocarbonyl lower alkylthio group is produced by reacting carboxylic acid (Ig) or reactive derivative thereof and amine (XI).

The reaction is performed in the same way as Processes B, C and E.

When a compound whose heterocyclic ring has plural carboxy groups is used as raw material, a product wherein the carboxy groups are wholly or selectively reacted can be obtained.

Process G:

A free carboxylic acid compound (Ij) can be easily produced by hydrolysis of corresponding ester compound (Ii).

In the reaction, a conventional hydrolysis in the presence of base such as sodium carbonate, sodium hydroxide, etc., or acid such as trifluoroacetic acid, hydrochloric acid, etc., can be applied.

When a compound whose heterocyclic ring has plural esters is used as the raw material, a product wherein all the esters are hydrolyzed may be obtained.

Process H:

A compound (Ik) having no free mercapto group, carboxy group or reactive hydroxy group is produced by reacting dihydroxybenzene derivative (XII) or alkali metal substitution product thereof, with halogen compound (XIII).

The reaction can be performed as in Processes A and D wherein, in particular, compound in which Y^1 or Y^2 is an oxygen atom is used.

Process I:

A compound of this invention wherein A is a 2-hydroxy lower alkylene group can be produced by reacting epoxy compound (XIV) and

hydroxy or mercapto compound (having no other mercapto group) or alkali metal substitution product thereof.

The reaction can be substantially as in Processes A, D, and H, i.e. using the compounds (XIV) and (XV) in almost equimolar amounts, or with excess of one, in an organic solvent inactive to the reaction, such as dimethylformamide, dimethylsulfoxide, methanol, ethanol, propanol, acetone, ethyl methyl ketone, tetrahydrofuran, chloroform, dioxane, etc. When a free hydroxy compound or mercapto compound is used as compound (XV), the reaction is performed in the presence of a base such as potassium carbonate, Triton B, potassium hydroxide, sodium hydroxide, sodium hydride, etc., preferably under water-free conditions.

Process J:

Contrary to the case of Process G, ester compound (Ii) is synthesized by reacting carboxylic acid (Ij) or reactive derivative thereof with lower alcohol (XVI) or reactive derivative thereof (such as a lower alkyl halide, etc.).

The reaction can be accomplished easily in conventional manner.

The compounds of this invention produced by the various processes described above can be isolated and

purified by conventional operations such as extraction, recrystallization, column chromatography, etc.

The compounds of this invention strongly antagonize the actions of SRS-A as described hereinbefore and hence are useful for the prophylaxis and treatment of various allergic diseases (e.g., bronchial asthma, allergic rhinitis, urticaria, etc.), ischemic heart diseases and ischemic brain diseases, inflamations, etc., caused by SRS-A.

At least some compounds of this invention also inhibit the production and release of SRS-A and have bronchodilator action. Compounds of this invention may also be useful as anti-ulcer agents.

Inhibition of SRS-A- and LTD_4-induced contraction of guinea pig ileum and trachea

Method: Male Hartley guinea-pigs weighing 500 to 700 g were killed by a blow on the head. The ileum and tracheal strips prepared according to the method of Constantine (1965) were suspended with 1.0 g tension in an organ bath containing 10 ml of Tyrode solution equilibrated with a mixture of 95% O_2 and 5% CO_2 at 37°C. The tissues were equilibrated for 60 min.; during this period the Tyrode solution was replaced

every 15 min. and the loading tension was adjusted to 1.0 g. The developed tension of the tissues was measured isometrically with a strain gauge transducer, and recorded on a Recticorder. Both the contractile response of the ileum to submaximal concentration of SRS-A (derived from guinea-pig lung) and the tracheal response to 10^{-8} M LTD_4 were measured in the absence and then the presence of various concentrations of test compounds. The incubation time of the compounds was 20 min.

Table 1

Example No.	Anti-SRS-A GP ileum IC50 (M)	Example No.	Anti-SRS-A GP ileum IC50 (M)
2	1.8×10^{-7}	36	1.4×10^{-7}
7	1.1×10^{-7}	37	5.2×10^{-8}
21	6.0×10^{-8}	38	3.8×10^{-8}
23	1.5×10^{-7}	41	6.4×10^{-8}
24	1.9×10^{-7}	42	1.3×10^{-7}
26	1.2×10^{-7}	44	1.3×10^{-7}
27	1.9×10^{-7}	46	1.1×10^{-7}
33	9.1×10^{-8}	51	1.6×10^{-7}

Table 2

Example No.	Anti-LTD_4 GP trachea IC50 (M)
21	1.3×10^{-7}
38	2.3×10^{-7}
51	4.2×10^{-7}

<u>Inhibition of SRS-A-mediated anaphylactic asthma in conscious guinea-pigs</u>

Method: Male Hartley guinea-pigs weighing 370 to 410 g were passively sensitized by intravenously injecting 1 ml/kg of rabbit anti-bovine serum albumin serum (PHA titer: 20480). Twenty-four hours after the sensitization, indomethacine (2 mg/kg), mepyramine (2 mg/kg) and propranolol (0.3 mg/kg) were injected into the saphenous vein 20, 5 and 5 min., respectively, prior to the antigen challenge. Thén, animals were placed in an 11 liter chamber connected to a glass nebulizer, and 1% solution of bovin serum albumin was sprayed into the chamber for 30 seconds. The animals were exposed to the antigen aerosol for 2 min. and observed for 15 min. after challenge. The time from the start of inhalation to the onset of cough and the mortality were recorded. Test compounds were orally administered 30 min. before antigen challenge.

Result: Compound of Example 21 at 3 mg/kg p.o. tended to inhibit the SRS-A-mediated anaphylactic asthma in conscious guinea-pigs, but this effect was not significant (Table 3). At doses of 10 mg/kg p.o. or higher,

compound of Example 21 significantly inhibited the SRS-A-mediated anaphylactic asthma.

Table 3

Effect of Compound of Example 21 on SRS-A-mediated anaphylactic asthma in conscious guinea-pigs[a)]

Compound[b)]	Dose (mg/kg p.o.)	N	Time to onset of cough (sec)	Mortality
Control	-	8	293 ± 22	6/8
Compound[c)]	3	8	377 ± 51	5/8
Control	-	8	281 ± 19	2/8
Compound[c)]	10	8	397 ± 42*	2/8*
Control	-	8	281 ± 11	7/8
Compound[c)]	30	8	457 ± 42**	2/8*

a): Animals were pretreated with mepyramine (2 mg/kg i.v.), propranolol (0.3 mg/kg i.v.) and indomethacine (2 mg/kg i.v.) 5, 5 and 20 min., respectively, prior to antigen challenge.

b): Test compound was orally administered 30 min. before antigen challenge.

c): Compound of Example 21.

* : $p < 0.0$, ** $p < 0.01$: Significantly differed from the value of the control group.

Toxicity

The minimum fatal dose of orally administered compound of Example 21 for mice and rats was more than 1000 mg/kg in each case.

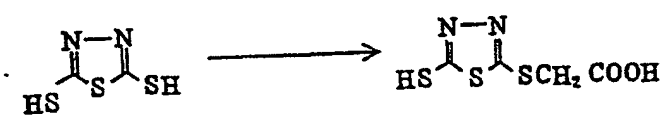
The compounds of this invention can be orally or parenterally administered as they are or as medical

compositions of these compounds and pharmaceutically permissible carriers or excipients (e.g., tablets, capsules, powders, granules, pills, ointments, syrups, injections, inhalants, suppositories, etc.). The dose depends upon the patient, administration route, symptoms, etc., but is usually 0.1 to 500 mg, preferably 1 to 200 mg, per adult per day orally or parenterally administered 2 or 3 times per day.

The invention is illustrated by the following Examples.

In addition, the production of starting compounds used in these Examples is shown in the following Reference Examples, wherein nPr means an n-propyl group.

Reference Example 1

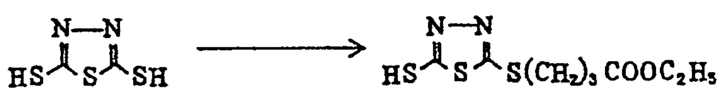


After stirring a mixture of 60 g of 2,5-dimercapto-1,3,4-thiadiazole, 25 g of potassium hydroxide, and 750 ml of ethanol for one hour at 70°C, 68 g of ethyl α-bromoacetate was added to the mixture and then the resultant mixture was refluxed for 2 hours. After cooling the reaction mixture, insoluble matters were filtered off and the filtrate thus formed was concentrated under reduced pressure. To the residue thus formed was added 600 ml of

10% sodium hydroxide. The mixture was stirred for one hour at 80°C. After cooling, the reaction mixture was acidified by the addition of concentrated hydrcchloric acid (below pH 1) and crystals thus formed were collected by filtration, washed with water, and recrystallized from acetone to provide 60 g of [(5-mercapto-1,3,4-thiadiazol-2-yl)thio]acetic acid.

Melting point: 170°C.

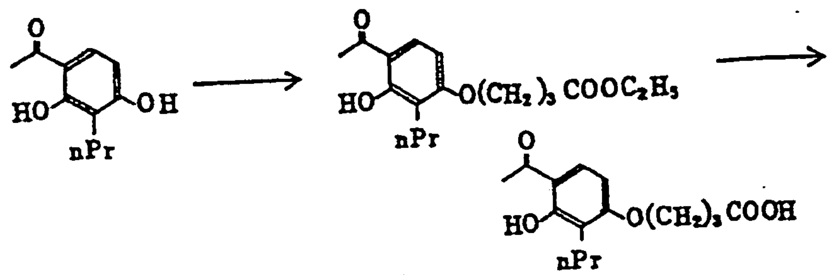
Reference Example 2



To a mixture of 3 g of 2,5-dimercapto-1,3,4-thiadiazole, 2.76 g of anhydrous potassium carbonate, and 10 ml of N,N-dimethylformamide was added 1 g of ethyl 4-bromobutyrate and the mixture was stirred overnight at room temperature. After addition of dilute hydrochloric acid to the reaction mixture, the product was extracted with ethyl acetate. The extract was washed with water, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue thus obtained was subjected to silica gel chromatography (using 200 ml of silica gel) and eluted with a mixture of toluene and ethyl acetate (9 : 1) to provide 0.95 g of ethyl 4-[(5-mercapto-1,3,4-thiadiazol-2-yl)thio]butyrate.

Melting point: 107 to 108°C

Reference Example 3

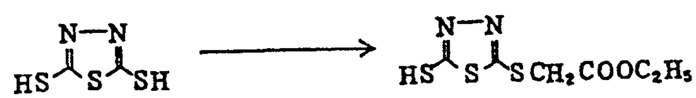


A mixture of 1.42 g of 2,4-dihydroxy-3-propylacetophenone, 2 g of ethyl 4-bromobutyrate, 1.5 g of potassium carbonate, and 10 ml of N,N-dimethylformamide was stirred overnight at room temperature. After addition of 100 ml of water to the reaction mixture, the product was extracted with 30 ml of toluene. The extract was washed with water, dried over anhydrous magnesium sulfate, and solvent was distilled off. The residue thus formed was subjected to silica gel column chromatography and eluted with toluene to provide 1.5 g of ethyl 4-(4-acetyl-3-hydroxy-2-propylphenoxy)butyrate as an oily product. In a solution of 2 g of potassium hydroxide in 40 ml of 80% methanol was dissolved 1.3 g of the oily product and the solution was allowed to stand for one hour. To the reaction mixture was added 20 ml of water and methanol was distilled off under reduced pressure. The aqueous solution thus obtained was acidified by 5% hydrochloric acid and extracted by ethyl acetate. The extract thus formed was washed with water and dried over anhydrous magnesium sulfate. The solvent was distilled off to

provide 1.1 g of 4-(4-acetyl-3-hydroxy-2-propylphenoxy)-butyric acid.

Melting point: 139 to 139°C.

Reference Example 4



In a mixture of 9.66 g of sodium hydroxide, 14.6 ml of water, and 122 ml of methanol was dissolved 36.3 g of 2,5-dimercapto-1,3,4-thiadiazole. After cooling the mixture, a solution of 24.1 ml of ethyl bromoacetate and 24 ml of methanol was added to the mixture below 10°C. The resultant mixture was stirred for 3 hours at room temperature and cooled below 10°C. 43.5 ml of water and 400 ml of 50% methanol were successively added to the reaction mixture, whereby crystals precipitated, and the mixture was allowed to stand overnight at 4°C. The crystals were collected by filtration, washed successively with water and then 50% methanol, and dried to provide 42.5 g of ethyl [(5-mercapto-1,3,4-thiadiazol-2-yl)thio]acetate.

Melting point: 67 to 68°C

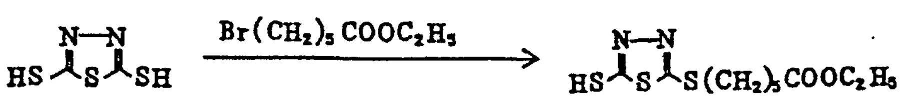
Reference Example 5

To a mixture of 10 g of 2,5-dimercapto-1,3,4-thiadiazole and 100 ml of methanol were added 2.6 g of sodium hydroxide and 5 ml of water. To the mixture was gradually added 9 g of ethyl 5-bromovalerate.

The resultant mixture was stirred for one hour at room temperature. The reaction mixture thus obtained was concentrated under reduced pressure. After addition of 100 ml of water the product was extracted with ethyl acetate. The extract thus formed was washed with water, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue was subjected to silica gel gel column chromatography and eluted with a mixture of toluene and ethyl acetate (9 : 1) to provide 10 g of ethyl 5-[(5-mercapto-1,3,4-thiadiazol-2-yl)thio]valerate.

Melting point: 53°C.

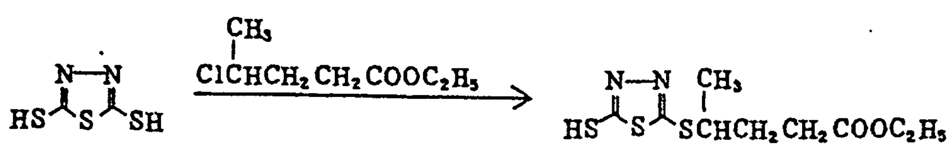
Reference Example 6



To a mixture of 7.6 g of 2,5-dimercapto-1,3,4-thiadiazole, 1.5 ml of water, 15 ml of methanol, and 2.0 g of sodium hydroxide was added 7.4 g of ethyl 6-bromohexanoate and the mixture was stirred for 2 hours at room temperature. After acidification of the resulting reaction mixture with dilute hydrochloric acid, 150 ml of water was added thereto. The mixture was extracted with toluene and the extract thus formed was washed with water, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue thus formed was recrystallized from a mixture of toluene and n-hexane to provide ethyl 6-[(5-mercapto-1,3,4-thiadiazol-2-yl)thio]hexanoate.

Melting point: 79 to 80°C.

Reference Example 7



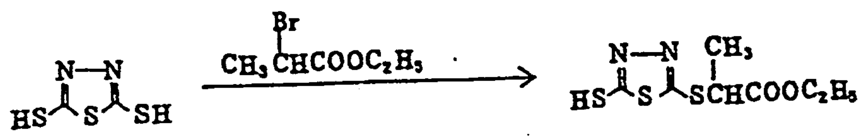
By following the same procedure as Reference Example 6 using 6.9 g of 2,5-dimercapto-1,3,4-thiadiazole and 5.8 g of ethyl 4-chlorovalerate as the starting materials, 1.5 g of ethyl 4-[(5-mercapto-1,3,4-thiadiazol-2-yl)thio]valerate was obtained as an oily product.

Nuclear magnetic resonance spectra ($CDCl_3$, TMS internal standard, ppm)

1.25(t, 3H), 1.45(d, 3H), 2.08(t, 2H), 2.52(t, 2H),

3.70(q, 1H), 4.15(q, 2H)

Reference Example 8

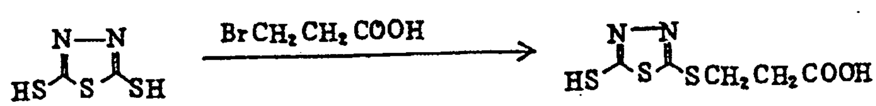


By following the same procedure as Reference Example 6 using 7.5 g of 2,5-dimercapto-1,3,4-thiadiazole and 5.8 g of ethyl 2-bromopropionate as the starting materials, 6.1 g of ethyl 2-[(5-mercapto-1,3,4-thiadiazol-2-yl)thio]propionate was obtained as an oily product.

Nuclear magnetic resonance spectra ($CDCl_3$, TMS internal standard, ppm)

1.28(t, 3H), 1.64(d, 3H), 4.0-4.80(m, 3H)

Reference Example 9

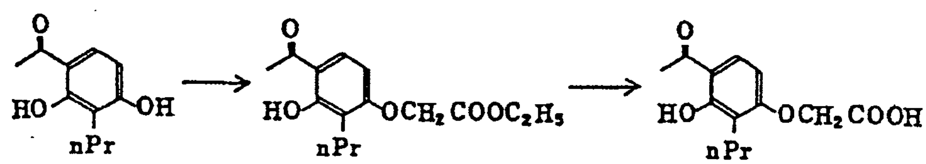


To a mixture of 1.5 g of 2,5-dimercapto-1,3,4-thiadiazole, 1.3 g of anhydrous potassium carbonate, and 20 ml of N,N-dimethylformamide was added 1.6 g of 3-bromopropionic acid, whereby the red color of the reaction mixture began to gradually fade and the reaction mixture became yellow. Then, the reaction mixture was poured into 100 ml of ice water and extracted with 30 ml of ethyl acetate three times. The

extract thus obtained was washed with water and extracted with 20 ml of an aqueous solution of 5% sodium hydrogen carbonate two times. The extract was washed with ethyl acetate, acidified with dilute hydrochloric acid, and extracted with 30 ml of ethyl acetate three times and the extract thus obtained was washed with water, dried over anhydrous sodium sulfate, and concentrated under reduced pressure to provide 0.76 g of 3-[(5-mercapto-1,3,4-thiadiazol-2-yl)thio]propionic acid.

Melting point: 105 to 108°C.

Reference Example 10



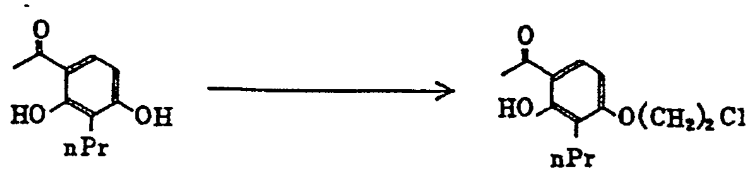
A mixture of 3 g of 2,4-dihydroxy-3-propylaceto-phenone, 2.5 g of ethyl bromoacetate, 2.3 g of anhydrous potassium carbonate, and 30 ml of methyl ethyl ketone was refluxed for 5 hours. Then, the solvent was removed under reduced pressure and after addition of 50 ml of toluene, the mixture was washed successively with water, dilute aqueous sodium hydroxide, and water, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue thus formed was recrystallized from a mixture of toluene and n-hexane to provide 2.8 g

of ethyl (4-acetyl-3-hydroxy-2-propylphenoxy)acetate (melting point: 66 to 66.5°C).

A mixture of the product thus obtained, 20 ml of methanol, and 8 ml of a 2N aqueous solution of sodium hydroxide was stirred for 2 hours at 50°C. Then, the reaction mixture thus obtained was concentrated under reduced pressure, mixed with 30 ml of water, and washed with toluene. The aqueous layer was acidified with dilute hydrochloric acid and extracted with ethyl acetate. The extract thus formed was washed with water, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue thus formed was recrystallized from isopropanol to provide 2.3 g of (4-acetyl-3-hydroxy-2-propylphenoxy)acetic acid.

Melting point: 140 to 141°C.

Reference Exmaple 11



A mixture of 1 g of 2,4-dihydroxy-3-propylacetophenone, 1.1 g of 1-bromo-2-chloroethane, 0.75 g of anhydrous potassium carbonate, and 0.05 g of tetra-n-butylammonium bromide was refluxed for 3 hours with vigorous stirring. After cooling, 30 ml of toluene was added to the reaction mixture and the mixture was washed with a dilute aqueous solution of sodium

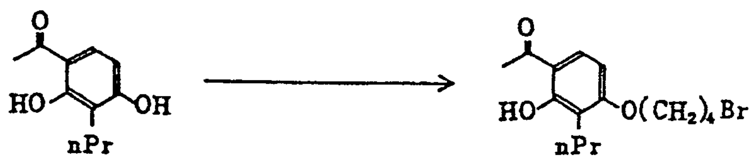
hydroxide, washed with water, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue thus formed was recrystallized from isopropanol to provide 0.46 g of 4-(2-chloroethoxy)-2-hydroxy-3-propylacetophenone.

Melting point: 73 to 74°C

Elemental analysis for $C_{13}H_{17}O_3Cl$:

	C	H	Cl
Calculated:	60.82%	6.67%	13.81%
Found:	60.67%	6.72%	13.76%

Reference Example 12

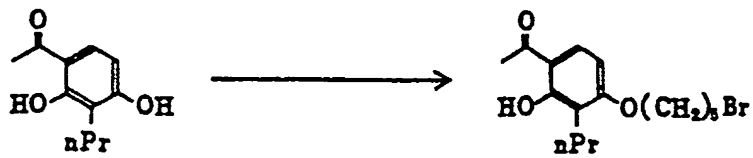


By following the same procedure as Reference Example 11 using 1 g of 2,4-dihydroxy-3-propylacetophenone and 4.5 g of 1,4-dibromobutane as starting materials followed by purification by silica gel column chromatography (Eluent: toluene), 1.3 g of 4-(4-bromobutoxy)-2-hydroxy-3-propylacetophenone was obtained as an oily product.

Nuclear magnetic resonance spectra ($CDCl_3$, TMS internal standard, ppm)

0.95(t, 3H), 1.10-1.80(m, 2H), 1.80-2.20(m, 4H), 2,58(s, 3H), 2,64(t, 2H), 3,52(t, 2H), 4,08(t, 2H), 6.42(d, 1H), 7.58(d, 1H), 12.7(s, 1H).

Reference Example 13

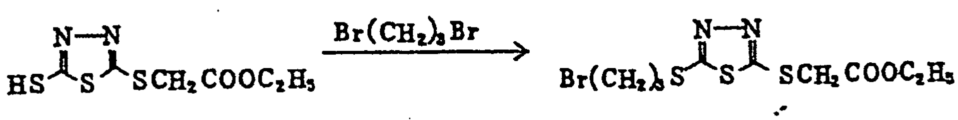


By following the same procedure as Reference Example 11 using 1 g of 2,4-dihydroxy-3-propylacetophenone and 4.7 g of 1,5-dibromopentane as the raw materials, 1.3 g of 4-(5-bromopentyloxy)-2-hydroxy-3-propylacetophenone was obtained as an oily product.

Nuclear magnetic resonance spectra ($CDCl_3$, TMS internal standard, ppm)

0.94(t, 3H), 1.30-2.10(m, 8H), 2.56(s, 3H), 2.64(t, 2H), 3,46(t, 2H), 4,40(t, 2H), 6,42(d, 1H), 7.58(d, 1H), 12.72(s, 1H).

Reference Example 14

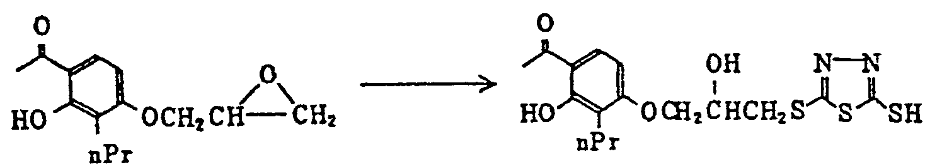


A mixture of 3 g of ethyl [(5-mercapto-1,3,4-thiadiazol-2-yl)thio]acetate, 9 g of 1,3-dibromopropane, 2.02 g of anhydrous potassium carbonate, 0.01 g of tetra-n-butylammonium bromide, and 20 ml of methyl ethyl ketone was vigorously stirred for 3 hours at 60°C. Toluene was added to the reaction mixture

and the resultant mixture was washed with water, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue thus formed was subjected to silica gel column chromatography and eluted with a mixture of toluene and ethyl acetate (9 : 1) to provide 1.35 g of ethyl [[5-(3-bromopropyl)thio-1,3,4-thiadiazol-2-yl]thio]acetate.

Melting point: 118 to 120°C.

Example 1

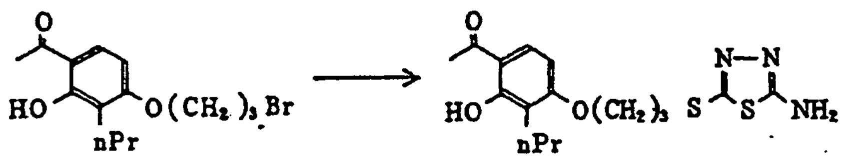


To a mixture of 600 mg of 2,5-dimercapto-1,3,4-thiadiazole, 560 mg of anhydrous potassium carbonate, and 10 ml of N,N-dimethylformamide was added 250 mg of 4-(2,3-epoxy)propoxy-2-hydroxy-3-propylacetophenone and the resultant mixture was stirred overnight at room temperature. To the reaction mixture thus obtained was added dilute hydrochloric acid and the product was extracted with toluene. The extract thus obtained was washed with water, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue was subjected to silica gel column chromatography and eluted with a mixture of toluene and ethyl acetate (4 : 1) to provide 260 mg of 2-hydroxy-4-[2-hydroxy-3-[(5-mercapto-1,3,4-thiadiazol-2-yl)thio]-propoxy]-3-propylacetophenone as an oily product.

Nuclear magnetic resonance spectra ($CDCl_3$, TMS internal standard, ppm)

0.92(t, 3H), 1.2-1.8(m, 2H), 2.56(s, 3H), 2,63(t, 2H), 3,48(dd, 2H), 4.0-4.2(m, 2H), 4.2-4.6(m, 1H), 6,42(dd, 1H), 7.61(d, 1H), 12.7(s, 1H).

Example 2



A mixture of 2 g of 4-(3-bromopropoxy)-2-hydroxy-3-propylacetophenone, 1.6 g of 2-amino-5-mercapto-1,3,4-thiadiazole, 1.6 g of potassium carbonate, and 20 ml of N,N-dimethylformamide was stirred for one hour at 20 to 30°C and after addition of 100 ml of water to the reaction mixture thus obtained, the product was extracted with ethyl acetate. The extract was washed with water, dried over anhydrous magnesium sulfate, and then the solvent was distilled off. The residue thus formed was subjected to silica gel column chromatography and eluted with toluene to provide 2.3 g of 4-[3-[(5-amino-1,3,4-thiadiazol-2-yl)thio]propoxy]-2-hydroxy-3-propylacetophenone.

Melting point: 144 to 145°C

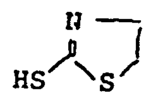
Elemental analysis for $C_{16}H_{21}N_3O_3S_2$:

	C	H	N	S
Calculated:	52.29%	5.76%	11.43%	17.45%
Found:	52.09%	5.71%	11.58%	17.61%

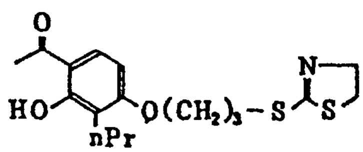
Examples 3 to 13

By following the same procedure as Example 2 the following compounds were obtained:

Example 3

Starting compound: 

Desired compound: 2-Hydroxy-3-propyl-4-[3-[(2-thiazolin-2-yl)thio]propoxy]acetophenone



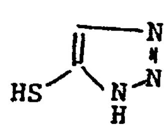
Physicochemical properties:

1) Oily product

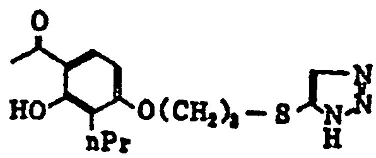
ii) Nuclear magnetic resonance spectra (TMS, $CDCl_3$, ppm)

0.92(3H, t, J=6Hz), 1.2-1.8(2H), 2.0-2.8(4H), 2,55(3H, s), 3.2-3.5(4H), 4.0-4.3(4H), 6.38 (1H, d, J=9Hz), 7.56(1H, d, J=9Hz), 12.7(1H).

Example 4

Starting compound: 

Desired compound: 2-Hydroxy-3-propyl-4-[3-[(1H-1,2,3-triazol-4-yl)thio]propoxy]acetophenone



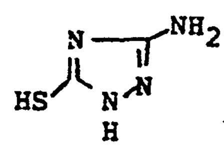
Physicochemical properties:

i) Oily product

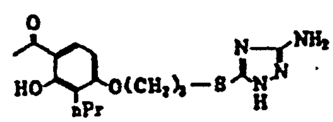
ii) Nuclear magnetic resonance spectra (TMS, $CDCl_3$, ppm)

0.8-1.1(3H), 1.2-1.8(2H), 2.0-2.8(5H), 2.55 (3H, s), 3.0-3.2(1H), 3.9-4.3(2H), 4.5-4.7 (1H), 6.3-6.4(1H), 7.5-7.6(2H), 12.8(1H)

Example 5

Starting compound: 

Desired compound: 4-[3-[(5-Amino-2H-1,2,4-triazol-3-yl)thio]propoxy]-2-hdyroxy-3-propyl-acetophenone



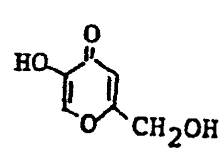
Physicochemical properties:

i) Melting point: 171 to 172°C

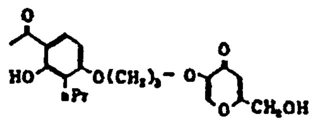
ii) Elemental analysis for $C_{16}H_{22}N_4O_3S$:

	C	H	N
Calculated:	54.84%	6.33%	15.99%
Found:	55.07%	6.62%	15.77%

Example 6

Starting compound: 

Desired compound: 2-Hydroxy-4-[3-[(6-hydroxymethyl-4-oxo-4H-pyran-3-yl)oxy]propoxy]-3-propylacetophenone



Physicochemical Properties:

i) Melting point: 84 to 87°C

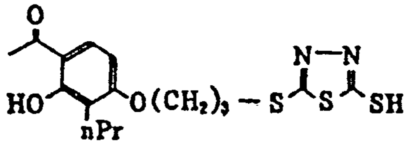
ii) Elemental analysis for $C_{20}H_{24}O_7$:

	C	H
Calculated:	63.82%	6.43%
Found:	63.73%	6.67%

Example 7

Starting compound:

Desired compound: 2-Hydroxy-4-[[3-(5-mercapto-1,3,4-thiadiazol-2-yl)thio]propoxy]-3-propylacetophenone



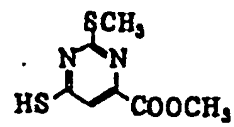
Physicochemical Properties:

i) Melting point: 127 to 129°C

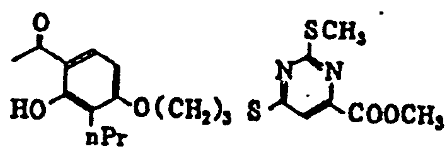
ii) Elemental analysis for $C_{16}H_{20}N_2O_3S_3$:

	C	H	N	S
Calculated:	49.97%	5.24%	7.28%	25.02%
Found:	50.00%	5.33%	7.19%	24.82%

Example 8

Starting compound: 

Desired compound: Methyl 6-[[3-(4-acetyl-3-hydroxy-2-propylphenoxy)propyl]thio]-2-methylthio-4-pyrimidinecarboxylate



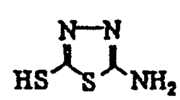
Physicochemical properties:

i) Melting point: 99 to 100°C

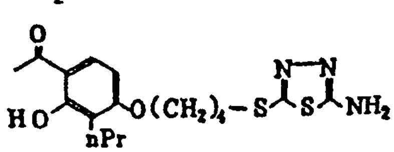
ii) Nuclear magnetic reasonace spectra (TMS, $CDCl_3$, ppm)

1.93 (3H, t, J=6Hz), 1.3-1.7(2H), 2.0-2.8(4H), 2.55(3H, s), 2.58 (3H, s), 3.3-3.5(2H), 3.92 (3H, s), 4.0-4.3(2H), 6.4-7.7(3H), 12.7(1H)

Example 9

Starting compound: 

Desired compound: 4-[4-[(2-Amino-1,3,4-thiadiazol-5-yl)thio]butoxy]-2-hydroxy-3-propylacetophenone



Physicochemcial properties:

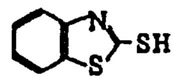
i) melting point: 107 to 108°C

ii) Elemental analysis for $C_{17}H_{23}N_3O_3S_2$:

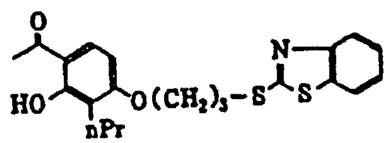
	C	H	N	S
Calculated:	53.52%	6.08%	11.01%	16.81%
Found:	53.24%	5.89%	10.97%	16.74%

Example 10

Starting compound:



Desired compound: 4-[3-(2-Benzothiazolylthio)-propoxy]-2-hydroxy-3-propylacetophenone



Physicochemical properties:

i) Oily product

ii) Elemetal analysis for $C_{21}H_{23}NO_3S_2$:

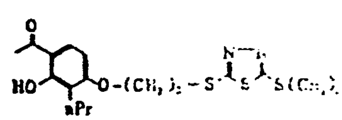
	C	H	N
Calculated:	62.81%	5.77%	3.49%
Found:	62.98%	5.98%	3.36%

Example 11

Starting compound:

Compound of Reference Example 2

Desired compound: Ethyl 4-[[5-[[3-(4-acetyl-3-hydroxy-2-propylphenoxy)propyl]thio]-[illegible] thiadiazol-2-yl]thio]butyrate



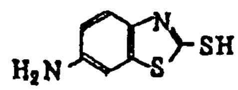
Physicochemical properties:

i) Oily product

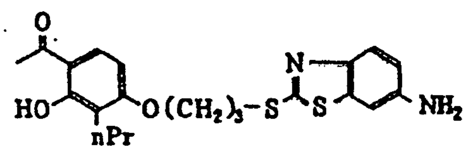
ii) Elemental analysis for $C_{22}H_{30}N_2O_5S_3$:

	C	H	N	S
Calculated:	52.99%	6.06%	5.62%	19.29%
Found:	52.99%	6.11%	5.53%	19.18%

Example 12

Starting compound: 

Desired compound: 4-[3-[(6-Aminobenzothiazol-2-yl)thio]propoxy]-2-hydroxy-3-propylacetophenone



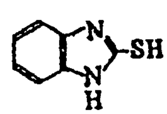
Physicochemical properties:

i) Oily product

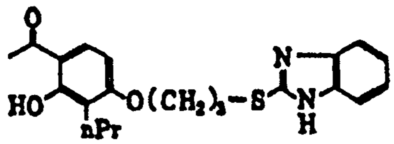
ii) Nuclear magnetic reasonacen spectra ($CDCl_3$, TMS, ppm)

1.95(s,3H), 1.2-2.0(2H,), 2.53(s, 3H), 2.0-2.9(4H), 4.48(t,3H), 3.4-4.0(2H, $-NH_2$), 4.17(t,3H), 6.2-7.8(5H), 12.70(1H)

Example 13

Starting compound: 

Desired compound: 4-[3-(2-Benzimidazolylthio)-propoxy]-2-hydroxy-3-propylacetophenone



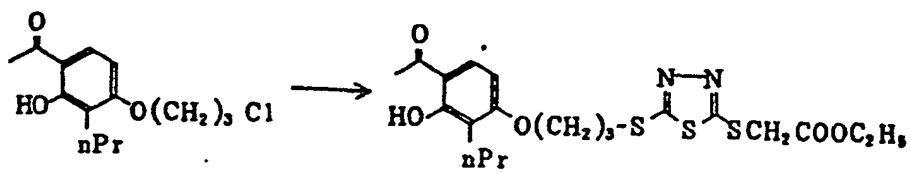
Physicochemcial Properties:

i) Melting point: 143 to 146°C

ii) Elemental analysis for $C_{21}H_{24}N_{2}O_{3}S$:

	C	H	N
Calculated:	65.60%	6.29%	7.29%
Found:	65.46%	6.34%	7.25%

Example 14



A mixture of 21.87 g of 4-(3-chloropropoxy)-2-hydroxy-3-propylacetophenone, 18.18 g of ethyl [(5-mercapto-1,3,4-thiadiazol-2-yl)thio]acetate, 12.7 g of anhydrous potassium carbonate, and 80 ml of methyl ethyl ketone was refluxed for 2.5 hours with vigorous stirring. After cooling, insoluble matters were filtered off and the filtrate was concentrated under reduced pressure. To the residue thus formed were added 200 ml of ethyl acetate and 150 ml of toluene and the mixture was washed with a dilute aqueous solution of sodium hydroxide and water, dried over anhydrous magnesium sulfate, and then concentrated under reduced pressure. The residue thus obtained was subjected to silica gel column chromatography and eluted with a mixture of toluene and ethyl acetate (10 : 1) to provide 33 g of ethyl [[5-[[3-(4-acetyl-3-hydroxy-2-propylphenoxy)propyl]thio]-1,3,4-thiadiazol-2-yl]thio]acetate.

Melting point: 71 to 72.5°C

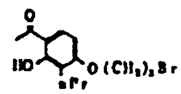
Elemental analysis for $C_{20}H_{26}N_2O_5S_3$:

	C	H	N	S
Calculated:	51.04	5.57%	5.95%	20.44%
Found:	51.07%	5.49%	5.79%	20.17%

Examples 15 to 18

By following the procedure of Example 14, the following compounds were prepared.

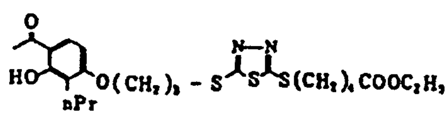
Example 15

Starting compound: 

and the compound of

Reference Example 5

Desired compound: Ethyl 5-[[5-[[3-(4-acetyl-3-hydroxy-2-propylphenoxy)propyl]thio]-1,3,4-thiadiazol-2-yl]thio]valerate



Physicochemical properties:

i) Oily product

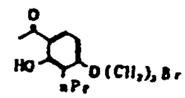
ii) Nuclear magnetic resonance spectra

($CDCl_3$, TMS, ppm)

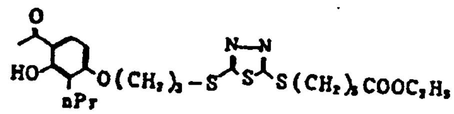
0.92(t, 3H), 1.24(t, 3H), 1.50-2.0(m, 6H), 2.34(2H), 2.54(s, 3H), 3,28(t, 2H), 3,46(t, 2H), 3.8-4.4(4H), 6.42(d, 1H), 7.58(d, 1H), 12.68(s, 1H)

Example 16

Starting compound: Compound of Reference Example 6 and



Desired compound: Ethyl 6-[[5-[[3-(4-acetyl-3-hydroxy-2-propylphenoxy)propyl]thio]-1,3,4-thiadiazol-2-yl]thio]hexanoate



Physicochemical properties:

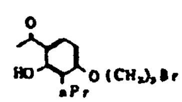
i) Oily product

ii) Nuclear magnetic reasonance spectra ($CDCl_3$, ppm)

0.92(t,3H), 1.24(t,3H), 1.3-2.0(8H), 2.1-2.5 (4H), 2.54(s, 3H), 3.28(t,2H), 3.48(t,2H), 4.0-4.3(4H), 6.43(d,1H), 7.60(d, 1H), 12.7 (s.1H)

Example 17

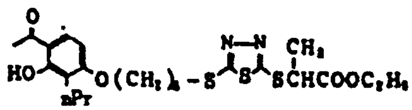
Starting compound:



and

Compound of Reference Example 8

Desired compound: Ethyl 2-[[5-[[3-(4-acetyl-3-hydroxy-2-propylphenoxy)propyl]thio]-1,3,4,-thiadiazol-2-yl]thio]propionate



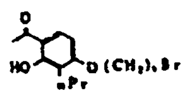
Physicochemcical properties:

i) Oily product

ii) Elemental analysis for $C_{21}H_{28}N_2O_5S_3$:

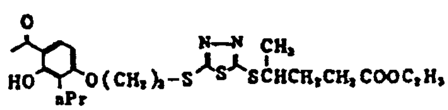
	N	S
Calculated:	5.78%	19.85%
Found:	5.85	20.05%

Example 18

Starting compound:  and

· Compound of Reference example 7

Desired compound: Ethyl 4-[[5-[[3-(4-acetyl-3-hydroxy-2-propylphenoxy)propyl]thio]-1,3,4-thiadiazol-2-yl]thio]valerate



Physicochemical properties:

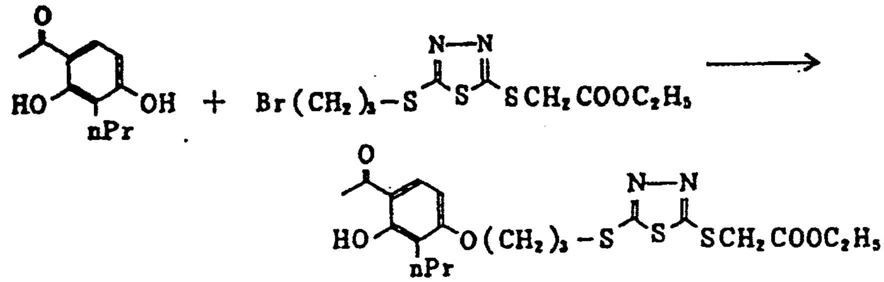
i) Oily product

ii) Nuclear magnetic reasonacne spectra

($CDCl_3$, TMS, ppm)

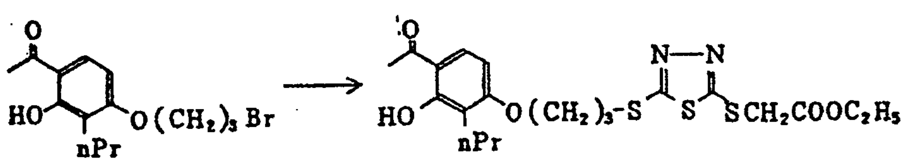
0.97(t,3H), 1.26(t,3H), 1.50 (d, 3H), 1.40-1.80(2H), 2.36(t,2H), 2.60(s,3H), 3.52 (t, 2H), 3.90(q,1H), 4.0-4.4(4H), 6.46(d,1H), 7.63(d,1H0, 12.7(s, 1H)

Example 19



Following the same procedure as Example 14 using 0.45 g of 2,4-dihdyroxy-3-propylacetophenone and 0.75 g of ethyl [[5-(3-bromopropyl)thio-1,3,4-thiadiazol-2-yl]thio]acetate gave 0.2 g of ethyl [[5-[[3-(4-acetyl-3-hydroxy-2-propylphenoxy)propyl]-thio]-1,3,4-thiadiazol-2-yl]thio]acetate. The properties of the product obtained were the same as those of the product obtained in Example 14.

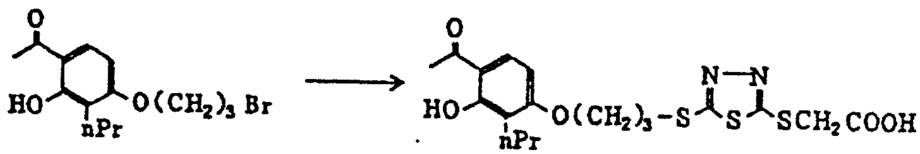
Example 20



A mixture of 596 mg of 4-(3-bromopropoxy)-2-hydroxy-3-propylacetophenone, 372.4 mg of ethyl [(5-mercapto-1,3,4-thiadiazol-2-yl)thio]acetate, 326 mg of anhydrous potassium carbonate, and 5 ml of N,N-dimethylformamide was stirred for 2 hours at room temperature. The reaction mixture thus obtained was concentrated under reduced pressure and after addition of chloroform, the mixture was washed with water, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue

thus formed was subjected to silica gel column chromatography and eluted with a mixture of toluene and ethyl acetate (10 : 1) to provide 663.3 mg of ethyl [[5-[[3-(4-acetyl-3-hydroxy-2-propoxyphenoxy)propyl]thio]-1,3,4-thiadiazol-2-yl]thio]acetate. The properties of the compound thus obtained were the same as those of the compound obtained in Example 14.

Example 21



A mixture of 3.1 g of 4-(3-bromopropoxy)-2-hydroxy-3-propylacetophenone, 2.4 g of [(5-mercapto-1,3,4-thiadiazol-2-yl)thio]acetic acid, 3 g of potassium carbonate, and 30 ml of N,N-dimethylformamide was stirred for 3 hours at room temperature. After addition of 150 ml of water to the reaction mixture obtained, the product was extracted with ethyl acetate. The separated aqueous layer was acidified with 10% hydrochloric acid, and extracted with ethyl acetate. The extract was washed with water, dried over anhydrous magnesium sulfate, and then the solvent was distilled off under reduced pressure to provide a solid material. The solid material was recrystallied from ethanol to provide 2.5 g of [[5-[[3-(4-acetyl-3-hydroxy-2-propylphenoxy)propyl]thio]-1,3,4-thiadiazol-2-yl]thio]acetic

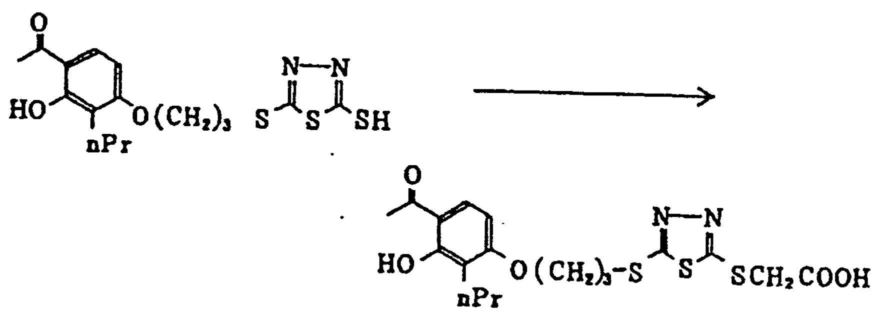
acid.

Melting point: 129 to 130°C

Elemental analysis for $C_{18}H_{22}N_2O_5S_3$:

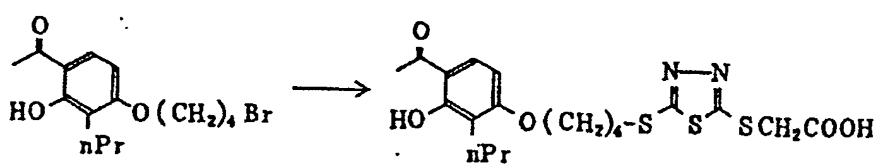
	C	H	N	S
Calculated:	48.85%	5.01%	6.33%	21.74%
Found:	48.78%	5.13%	6.29%	21.49%

Example 22



By following the same procedure as Example 21 using 100 mg of 2-hydroxy-4-[[-(5-mercapto-1,3,4-thiadiazol-2-yl)thio]propoxy]-3-propylacetophenone obtained in Example 7 and 40 mg of bromoacetic acid as the starting materials, 70 mg of [[5-[[3-(4-acetyl-3-hydroxy-2-propylphenoxy)propyl]-thio]-1,3,4-thiadiazol-2-yl]thio] acetic acid was obainted. The compound thus obtained had the same properties as those of the compound obtained in Example 21.

Example 23



A mixture of 1.3 g of 4-(4-bromobutoxy)-2-hydroxy-3-propylacetophenone, obtained in Reference Example 12, 1.0 g of [5-mercapto-1,3,4-thiadiazol-2-yl)thio]acetic acid, 1.0 g of anhydrous potassium carbonate, and 5 ml of N,N-dimethylformamide was stirred for 3 hours at 50°C. The reaction mixture thus obtained was mixed with 30 ml of water, washed with toluene, acidified with dilute hydrochloric acid, and extracted with ethyl acetate. The extract thus formed was washed with water, dried under anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue thus formed was recrystallized from ethyl acetate to provide 1.15 g of [[5-[[4-(4-acetyl-3-hydroxy-2-propylphenoxy)butyl]thio]-1,3,4-thiadiazol-2-yl]thio]acetic acid.

Melting point: 123 to 124.5°C.

Elemental analysis for $C_{19}H_{24}N_2O_5S_3$:

	C	H	N	S
Calculated:	49.98%	5.30%	6.14%	21.07%
Found:	49.76%	5.29%	6.07%	21.13%

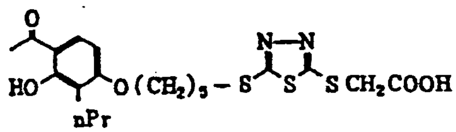
Examples 24 to 27

By following the procedure of Example 23, the following compounds were prepared:

Example 24

Starting compound: The compound of Reference Example 1 and the compound of Reference Example 13

Desired compound: [[5-[[5-(4-Acetyl-3-hydroxy-2-propylphenoxy)pentyl]thio]-1,3,4-thiadiazol-2-yl]thio]acetic acid



Physicochemical properties:

i) Melting point: 107 to 108°C

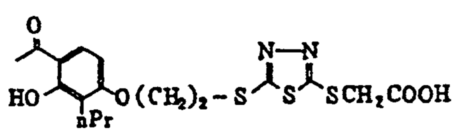
ii) Elemental analysis for $C_{20}H_{26}N_2O_5S_3$

	C	H	N	S
Calculated:	51.04%	5.57%	5.95%	20.44%
Found:	50.81%	5.64%	5.98%	20.40%

Example 25

Starting compound: The compound of Reference Example 1 and the compound of Reference Example 11

Desired compound: [[5-[[2-(4-Acetyl-3-hydroxy-2-propylphenoxy)ethyl]thio]-1,3,4-thiadiazol-2-yl]thio]acetic acid



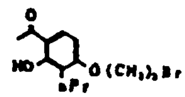
Physicochemical properties:

i) Melting point: 135 to 137°C

ii) Nuclear magnetic resonance spectra (DMSO-d_6, TMS, ppm)

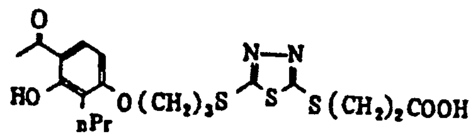
0.98(t, 3H), 1.44(m, 2H), 2.60(s, 3H), 3,72(t, 2H), 4.16(d, 2H), 4.40(t, 2H), 6.66 (d, 1H), 2.78(d, 1H), 12.81(s, 1H)

Example 26

Starting compound:  and

Compound of Reference example 1

Desired compound: 3-[[5-[[3-(4-acetyl-3-hydroxy-2-propylphenoxy)propyl]thio]-1,3,4-thiadiazol-2-yl]thio]propionic acid



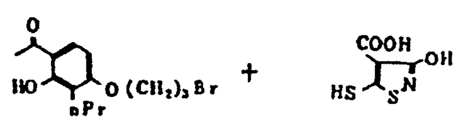
Physicochemical properties:

i) Melting point 102 to 104°C

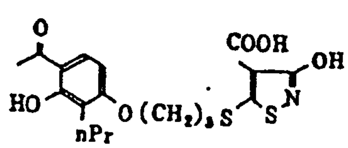
ii) Elemental analysis for $C_{19}H_{24}N_2O_5S_3$:

	N	S
Calculated:	6.14%	21.06%
Found:	6.28%	21.03%

Example 27

Starting compound: 

Desired compound: 5-[[3-(4-acetyl-3-hydroxy-2-propylphenoxy)propyl]thio]-3-hydroxy-4-isothiazol carboxylic acid



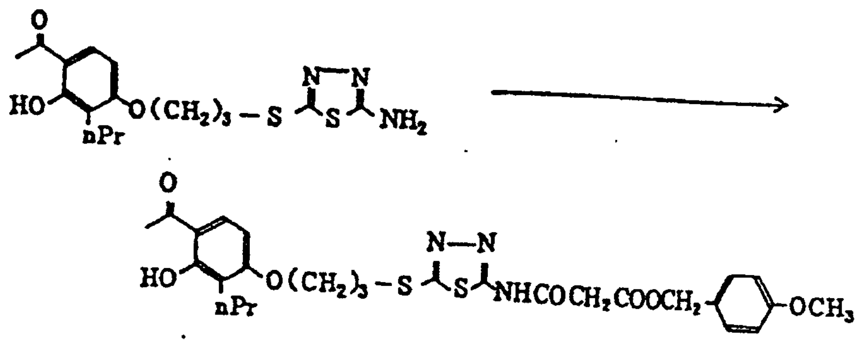
Physicochemical properties:

i) Melting point 182 to 184°C

ii) Elemental analysis for $C_{18}H_{21}NO_6S_2$:

	C	H	H	S
Calculated:	52.54%	5.14%	3.40%	15.58%
Found:	52.23%	4.96%	3.20%	15.48%

Example 28



To a solution of 0.28 g of 4-[3-[(5-amino-1,3,4-thiadiazol-2-yl)thio]propoxy]-2-hydroxy-3-propylacetophenone obtained in Example 2 dissolved in 5 ml of pyridine were added 0.28 g of mono-p-methoxybenzyl malonate, 0.20 g of dicyclohexylcarbodiimide, and 10 mg of p-toluenesulfonic acid, and the mixture obtained was stirred for 3 hours at room temperature. Insoluble matters were filtered off and the filtrate obtained was concentrated under reduced pressure. To the residue thus formed was added 30 ml of water and the product was extracted with 20 ml of toluene. The extract thus obtained was washed with water, dried over anhydrous magnesium sulfate, and then the solvent was distilled off to provide a solid material. The solid material was washed with methanol and dried to provide 0.25 g of p-methoxybenzyl 3-[[5-[[3-(4-acetyl-3-hydroxy-2-propylphenoxy)propyl]thio]-1,3,4-thiadiazol-2-yl]amino]-3-oxopropionate.

Melting point: 133 to 135°C

Elemental analysis for $C_{27}H_{31}N_3O_7S_2$:

	C	H	N	S
Calculated:	56.53%	5.45%	7.32%	11.18%
Found:	56.81%	5.46%	7.19%	10.96%

Examples 29 to 32

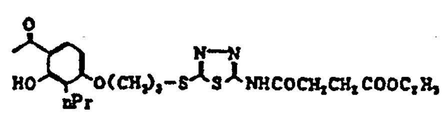
By following the same procedure as in Example 28, the following compounds were prepared:

Example 29

Starting compound: Compound of Example 2 and

$$\begin{array}{l} CH_2COOH \\ | \\ CH_2COOC_2H_5 \end{array}$$

Desired compound: Ethyl 4-[[5-[[3-(4-acetyl-3-hydroxy-2-propylphenoxy)propyl]thio]-1,3,4-thiadiazol-2-yl]amino]-4-oxobutyrate



Physicochemical properties:

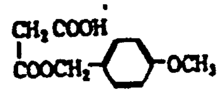
i) Melting point: 129 to 131°C

ii) Elemental analysis for $C_{22}H_{29}N_3O_6S_2$:

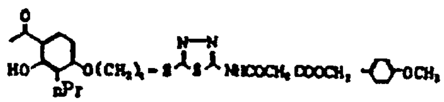
	C	H	N
Calculated:	53.32%	5.90%	8.48%
Found:	53.14	5.76	8.47

Example 30

Starting compound: Compound of Example 9 and



Desired compound: p-Methyoxybenzyl 3-[[5-[[3-(4-acetyl-3-hydroxy-2-propylphenoxy)butyl]-thio]-1,3,4-thiadiazol-2-yl]amino]-3-oxopropionate



Physicochemical properties:

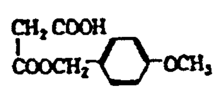
i) Melting point 141 to 143°C

ii) Nuclear magnetic resonance spectra ($CDCl_3$, TMS, ppm)

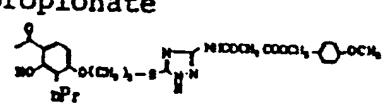
1.90(t,3H), 1.0-2.0(8H), 2.60(s,3H), 3.1-3.4(2H), 3.68(s,2H), 3.80(s,3H), 3.9-4.2 (2H), 5.12(s,2H), 6.15-7.4(7H), 12.7(s,1H)

Example 31

Starting compound: Compound of example of 4 and



Desired compound: p-Methoxybenzyl 3-[[2-[[3-(4-acetyl-3-hydroxy-2-propylphenoxy)propyl]-thio]-1H-1,2,4-triazol-3-yl]amino]-3-oxopropionate



Physicochemical properties:

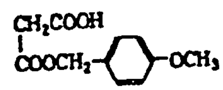
i) Melting point: 151 to 153°C

ii) Elemental analysis for $C_{27}H_{32}N_4O_7S$:

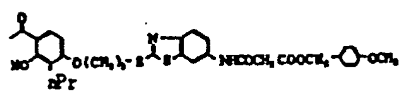
	C	H	N
Calculated:	58.26%	7.79%	10.07%
Found:	58.24%	5.83%	9.90%

Example 32

Starting compound: Compound of Example 11 and



Desired compound: p-Methoxybenzyl 3-[[2-[[3-(4-acetyl-3-hydroxy-2-propylphenoxy)propyl]-thio]benzothiazol-6-yl]amino]-3-oxopropionate



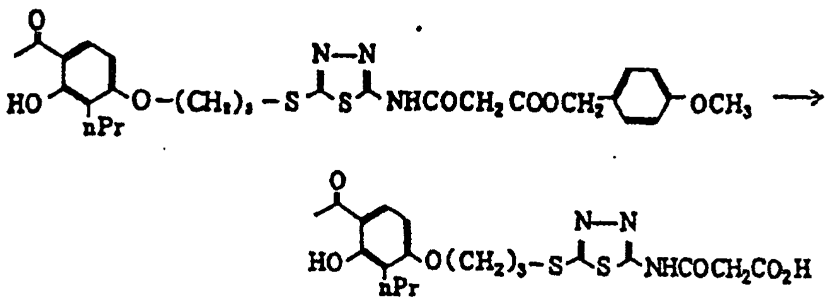
Physicochemical properties:

i) Melting point: 103 to 105°C

ii) Elemental analysis for $C_{32}H_{34}N_2O_7S_2$:

	C	H	N
Calculated:	61.72%	5.50%	4.50%
Found:	61.77%	5.44%	4.39%

Example 33



In a solution of 1.5 g of potassium hydroxide in 30 ml of 90% methanol was dissolved 0.9 g of p-methoxybenzyl ester obtained in Example 28 and the mixture was allowed to stand for 30 minutes at room temperature; 30 ml of water was added to the reaction mixture thus obtained. Then, méthanol was distilled off from the reaction mixture and the aqueous solution thus obtained was washed with 30 ml of ethyl acetate, acidified with 10% hydrochloric acid, and then extracted with 30 ml of ethyl acetate. The extract thus obtained was washed with water, dried over anhydrous magnesium sulfate, and then the solvent was distilled off to provide a solid material. The solid material was washed with chloroform and dried to provide 0.5 g of 3-[[5-[[3-(4-acetyl-3-hydroxy-2-propylphenoxy)propyl]thio]-1,3,4-thiadiazol-2-yl]amino]-3-oxopropionic acid.

Melting point: 172 to 174°C

Elemental analysis for $C_{19}H_{23}N_3O_6S_2$:

	C	H	N	S
Calculated	50.32%	5.11%	9.26%	14.14%
Found:	50.95%	5.01%	9.29%	13.93%

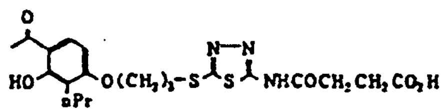
Examples 34 to 39

By following the procedure of Example 33, the following compounds were prepared.

Example 34

Starting compound: The compound of Example 29

Desired compound: 4-[[5-[[3-(4-Acetyl-3-hydroxy-2-propylphenoxy)propyl]thio]-1,3,4-thiadiazol-2-yl]amino]-4-oxobutyric acid



Physicochemical properties:

i) Melting point: 204 to 206°C

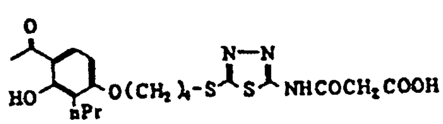
ii) Elemental analysis for $C_{20}H_{25}N_3O_6S_2$:

	C	H	N
Calculated:	51.38%	5.39%	8.99%
Found:	51.18%	5.37%	8.99%

Example 35

Starting compound: The compound of Example 30

Desired compound: 3-[[5-[[4-(4-Acetyl-3-hydroxy-2-propylphenoxy)butyl]thio]-1,3,4-thiadiazol-2-yl]amino]-3-oxopropionic acid.



Physicochemical properties:

i) Melting point: 168 to 170°C

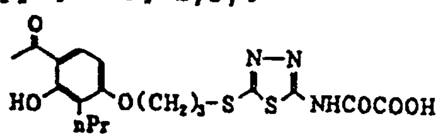
ii) Elemental analysis for $C_{20}H_{25}N_3O_6S_2$:

	C	H
Calculated:	51.38%	5.39%
Found:	51.60%	5.68%

Example 36

Starting compound: The compound of Example 46

Desired compound: N-[5-[[3-(4-Acetyl-3-hydroxy-2-propylphenoxy)propyl]thio]-1,3,4-thiadiazol-2-yl]oxamic acid



Physicochemical properties:

i) Melting point: 172 to 175°C (decompd.)

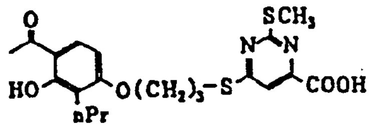
ii) Elemental analysis for $C_{18}H_{21}N_3O_6S_2$:

	C	H	N
Calculated:	49.19%	4.82%	9.56%
Found:	49.28%	4.80%	9.43%

Example 37

Starting compound: Compound of Exmple 7

Desired compound: 6-[[3-(4-Acetyl-3-hydroxy-2-propylphenoxy)propyl]thio]-2-methylthio-4-pyrimidinecarboxylic acid



Physicochemical properties:

i) Melting point: 125 to 128°C

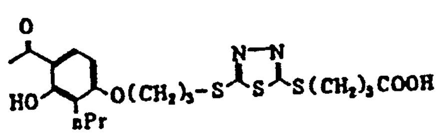
ii) Nuclear magnetic resonance spectra (TMS, $CDCl_3$ ppm)

0.92 (3H, t, J=6Hz), 1.2-1.8(2H), 2.1-2.8 (4H), 2.55(3H, s), 2.59(3H, s), 3.3.-3.6(2H) 4.1-4.3(2H), 6.42(1H, d, J=9Hz), 7.5-7.7(2H)

Example 38

Starting compound: Compound of Example 10

Desired compound: 4-[[5-[[3-(4-Acetyl-3-hydroxy-2-propylphenoxy)propyl]thio]-1,3,4-thiadiazol-2-yl]thio]butyric acid



Physicochemical properties:

i) Melting point: 100 to 101°C

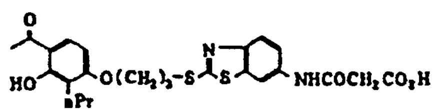
ii) Elemental analysis for $C_{20}H_{26}N_2O_5S_3$:

	C	H	N	S
Calculated:	51.04%	5.57%	5.95%	20.44%
Found:	51.18%	5.66%	5.74%	20.44%

Example 39

Starting compound: Compound of Example 32

Desired compound: 3-[[2-[[3-(4-Acetyl-3-hydroxy-2-propylphenoxy)propyl]thio]benzothiazol-6-yl]amino]-3-oxopropionic acid



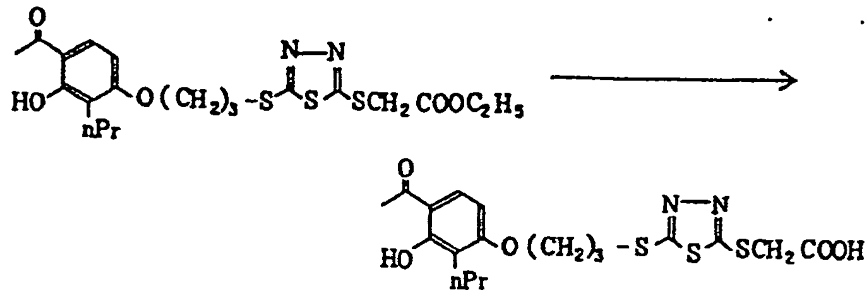
Physicochemical Properties:

i) Melting point: 148 to 150°C

ii) Elemental analysis for $C_{24}H_{26}N_2O_6S_2$:

	C	H	N
Calculated:	57.35%	5.21%	5.57%
Found:	57.18%	5.19%	5.56%

Example 40



To a mixture of 4.2 g of ethyl [[5-[[3-(4-acetyl-3-hydroxy-2-propylphenoxy)propyl]thio]-1,3,4-thiadiazol-2-yl]thio]acetate obtained in Example 14 and 30 ml of methanol was added 20 ml of 5% aqueous

sodium hdyroxide and the mixture was stirred for 30 minutes. Then, 30 ml of water was added to the reaction mixture and methanol was removed under reduced pressure. The residue thus formed was washed with ethyl acetate, acidified with dilute hydrochloric acid, and extracted with ethyl acetate. The extract was washed with water, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue thus formed was recrystallized from 90% ethanol to provide 3.07 g of [[5-[[3-(4-acetyl-3-hydroxy-2-propylphenoxy)propyl]thio]-1,3,4-thiadiazol-2-yl]thio]acetic acid. The properties of the compound thus obtained were the same as those of the compound obtained in Example 21.

Examples 41 to 45

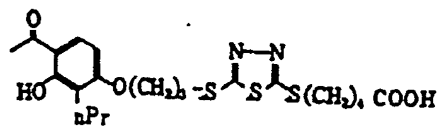
Example 41

By following the procedure of Example 40, the following compounds were prepared

Example 41

Starting compound: The compound of Example 15

Desired compound: 5-[[5-[[3-(4-Acetyl-3-hydroxy-2-propylphenoxy)propyl]thio]-1,3,4-thiadiazol-2-yl]thio]valeric acid



Physicochemical properties:

i) Melting point 86 to 87°C

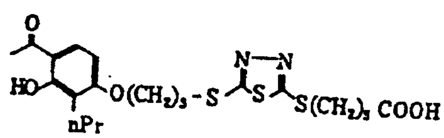
ii) Elemental analysis for $C_{21}H_{28}N_2O_5S_3$:

	C	H	N	S
Calculated:	52.04%	5.82%	5.78%	19.85%
Found:	51.82%	6.02%	5.72%	19.96%

Example 42

Starting compound: The compound of Example 16

Desired compound: 6-[[5-[[3-(4-Acetyl-3-hydroxy-2-propylphenoxy)propyl]thio]-1,3,4-thiadiazol-2-yl]thio]hexanoic acid



Physicochemical properties:

i) Melting point: 77 to 78°C

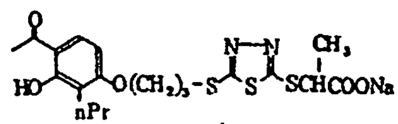
ii) Elemental analysis for $C_{22}H_{30}N_2O_3S \cdot \frac{1}{2}H_2O$

	C	H	N
Calculated:	52.15%	5.97%	5.53%
Found:	52.14%	5.21%	5.33%

Example 43

Starting compound: Compound of Example 17

Desired compound: Sodium 2-[[5-[[3-(4-acetyl-3-hydroxy-2-propylphenoxy)propyl]thio]-1,3,4-thiadiazol-2-yl]thio]propionic acid



Physicochemical properties:

i) Oily product

ii) Nuclear magnetic resonance spectra

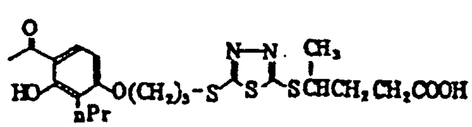
(DMSO-d_6, TMS, ppm)

0.88(t,3H), 1.52(d,3H), 2.20(2H), 2.60(s,3H), 3,44(t,2H), 4.22(t,2H), 6.66(d,1H), 7.84(d,1H), 12.8(s,1H),

Example 44

Starting compound: Compound of Example 18

Desired compound: 4-[[5-[[3-(4-Acetyl-3-hydroxy-2-propylphenoxy)propyl]thio]-1,3,4-thiadiazol-2-yl]thio]valeric acid



Physicochemical Properties:

i) Oily product

ii) Nuclear magnetic resonance spectra

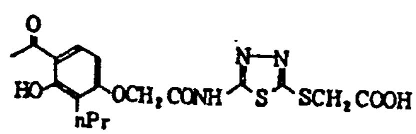
($CDCl_3$, TMS, ppm)

0.92(t, 3H), 1.49(d,3H), 2.12(t, 2H), 2.60 (s, 3H), 3.50(t,2H), 4.18(t, 2H), 6.45(d,1H), 7.61(d,1H), 12.7(s,1H)

Example 45

Starting compound: Compound of Example 50

Desired compound: [[5-[2-(4-Acetyl-3-hydroxy-2-propylphenoxy)acetamide]-1,3,4-thiadiazol-2-yl]thio]acetic acid



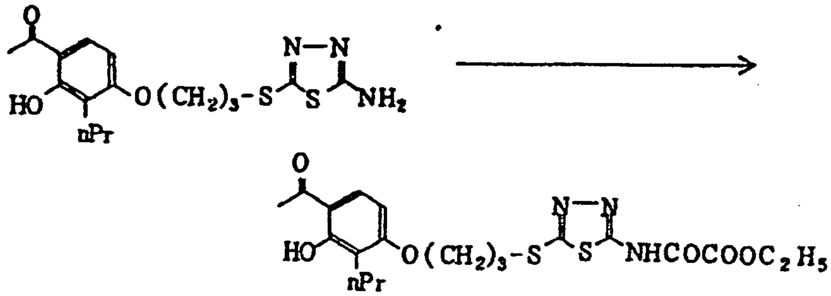
Physicochemical Properties:

i) Melting point: 224 to 226°C

ii) Elemental analysis for $C_{17}H_{19}N_3O_6S_2$:

	C	H	N	S
Calculated:	47.99%	4.50%	9.88%	15.07%
Found:	47.97%	4.41%	9.76%	14.94%

Example 46



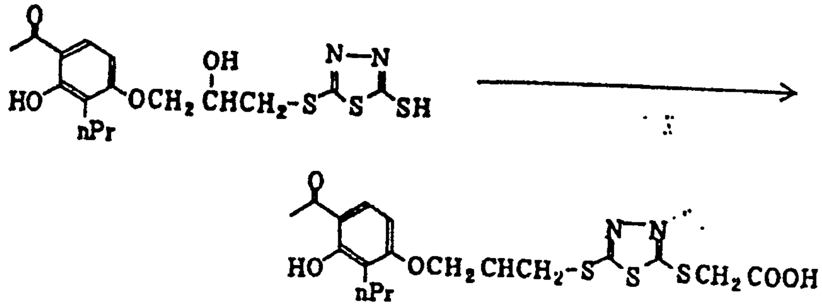
To a solution of 0.4 g of 4-[3-[(5-amino-1,3,4-thiadiazol-2-yl)thio]propoxy]-2-hydroxy-3-propylacetophenone (obtained in Example 2) dissolved in 10 ml of pyridine was added a mixture of 0.2 g of ethyloxalyl chloride and 1 ml of toluene under cooling below -10°C and then (the) resultant mixture was stirred for 30 minutes at room temperature. The reaction mixture thus obtained was mixed with 50 ml of water and extracted with 30 ml of ethyl acetate. The extract was successively washed with water, 5% hydrochloric acid, and then water, dried, and then the solvent was distilled off under reduced pressure. The residue thus formed was subjected to silica gel column chromatography and eluted (with) a mixture of toluene and ethyl acetate (3 : 2) to provide 0.3 g of ethyl N-[5-[[3-(4-acetyl-3-hydroxy-2-propylphenoxy)propyl]thio]-1,3,4-thiadiazol-2-yl]oxamate.

Melting point: 146 to 147°C

Elemental analysis for $C_{18}H_{21}O_6N_3S_2$:

	C	H	N	S
Calculated:	49.19%	4.82%	9.56%	14.59%
Found:	49.28%	4.80%	9.43%	14.56%

Example 47

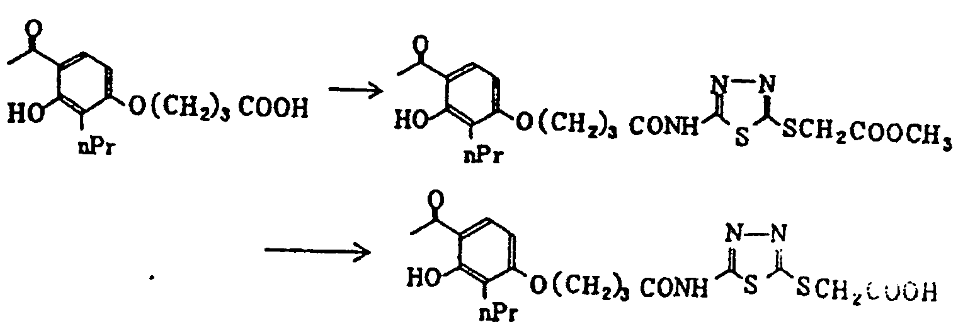


By following the same procedure as Example 22 using 2-hydroxy-4-[2-hydroxy-3-[(5-mercapto-1,3,4-thiadiazol-2-yl)thio]propoxy]-3-propylacetophenone obtained in Example 1 and bromoacetic acid as the starting materials, [[5-[[3-(4-acetyl-3-hydroxy-2-propylphenoxy)-2-hydroxypropyl]thio]-1,3,4-thiadiazol-2-yl]thio]acetic acid was obtained. Melting point: 72 to 75°C.

Nuclear magnetic resonance spectra ($CDCl_3$. TMS internal standard, ppm)

0.92(t, 3H), 1.3-1.8(m, 2H), 2.54(s, 3H), 2.60(t, 2H), 3,60(t, 2H), 4.04(s, 2H), 4.0-4.2(m, 2H), 4.2-4.6(m, 1H), 6.42(d, 1H), 7.60(d, 1H), 12.7(s, 1H).

Example 48



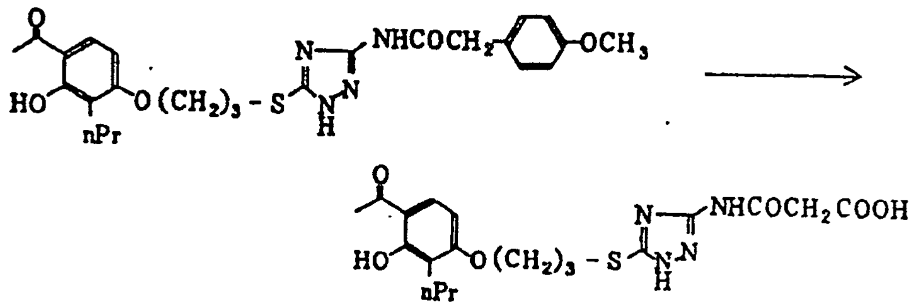
To a solution of 0.42 g of 4-(4-acetyl-3-hydroxy-2-propylphenoxy)butyric acid obtained in Reference Example 3 dissolved in 10 ml of pyridine were added 0.31 g of methyl [[5-amino-1,3,4-thiadiazol-2-yl)thio]-acetate, 0.4 g of dicyclohexylcarbodiimide, and 3 mg of p-toluenesulfonic acid and the mixture was stirred for 3 hours at room temperature. Insoluble matters were removed by filtration and the filtrate was concentrated. The solid residue thus formed was, without being purified, in a solution of 1 g of potassium hydroxide dissolved in 20 ml of 90% methanol and after filtering off insoluble matters, the filtrate was allowed to stand for 30 minutes at room temperature. To the reaction mixture thus obtained was added 20 ml of water and then methanol was distilled off under reduced pressure. The aqueous solution thus obtained was washed with 20 ml of ethyl acetate. The aqueous solution was acidified with 10% hydrochloric acid and extracted with ethyl acetate. The extract thus obtained was washed with water, dried over anhydrous magnesium sulfate, and then the solvent was distilled off to provide 0.3 g of [[5-[[4-(4-acetyl-3-hydroxy-2-propylphenoxy)butyrylamido]-1,3,4-thiadiazol-2-yl]-thio]acetic acid.

Nuclear magnetic resonance spectra ($CDCl_3$, DMSO-d_6, ppm)

0.87(3H, t), 1.1-1.7(2H), 2.57(3H, s), 1.9-3.0(6H), 4,07(2H, s), 4.11(2H, t), 6.61(1H, d), 7.78(1H, d),

12.80(1H, s)

Example 49



In a mixture of 1.5 ml of trifluoroacetic acid and 0.1 ml of anisole was dissolved 100 mg of p-methoxybenzyl 3-[[5-[[3-(4-acetyl-3-hydroxy-2-propylphenoxy)propyl]-thio]-1,3,4-thiadiazol-2-yl]amino]-3-oxopropionate obtained in Example 31 at 10 to 20°C and after stirring the solution thus obtained for 30 minutes, trifluoro-acetic acid was distilled off under reduced pressure. The residue thus formed was mixed with 20 ml of water and extracted with 20 ml of ethyl acetate. The extract was washed with water, dried over anhydrous magnesium sulfate, and then the solvent was distilled off to provide a solid product. The solid product was washed with methylene chloride and dried to provide 50 mg of 3-[[5-[[-3-(4-acetyl-3-hydroxy-2-propylphenoxy)propyl]-thio]-1,3,4-thiadiazol-2-yl]amino]-3-oxopropionic acid.

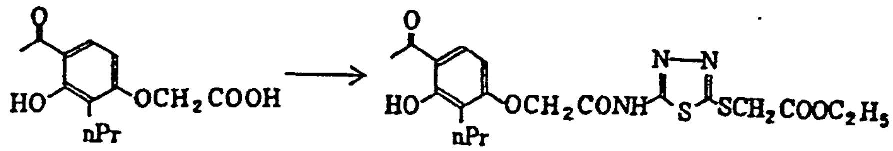
Melting point: 163 to 165°C

Nuclear magnetic resonance spectra ($CDCl_3$- DMSO-d_6 (10 : 1), TMS, ppm)

0.90(3H, t), 1.2-1.8(2H), 2.0-2.8(4H), 2.55(3H, s),

3.25(3H, t), 3.48(2H, s), 4.17(2H, t), 6.44(1H, d), 7.61(1H, d), 12.68(1H, s).

Example 50



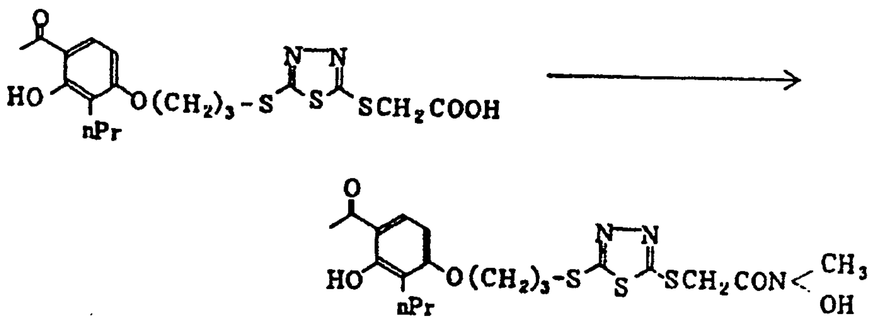
To a mixture of 0.7 g of (4-acetyl-3-hydroxy-2-propylphenoxy)acetic acid obtained in Reference Example 10, 0.6 g of ethyl [[5-amino-1,3,4-thiadiazol-2-yl]thio]acetate, 10 ml of pyridine, and 1 mg of p-toluenesulfonic acid was added 0.57 g of dicyclohexyl-carbodiimide and the mixture was stirred for one hour at room temperature. Insoluble matters were filtered off and the filtrate formed was concentrated under reduced pressure. To the residue thus formed was added ethyl acetate and the mixture was washed with dilute hydrochloric acid, washed with dilute aqueous sodium hydrogen carbonate, washed with water, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue thus formed was recrystallized from 2-methoxyethanol to provide 0.8 g of [[5-[2-(4-acetyl-3-hydroxy-2-propylphenoxy)acetoamide]-1,3,4-thiadiazol-2-yl]thio]acetic acid.

Melting point: 183 to 184°C

Elemental analysis for $C_{19}H_{23}N_3O_6S_2$:

	C	H	N	S
Calculated:	50.32%	5.11%	9.26%	14.14%
Found:	50.47%	5.14%	9.24%	14.38%

Example 51



To a mixture of 0.5 g of [[5-[[3-(4-acetyl-3-hydroxy-2-propylphenoxy)propyl]thio]-1,3,4-thiadiazol-2-yl]thio]acetic acid, 0.23 g of dicyclohexylcarbodiimide, 0.14 g of 1-hydroxybenzotriazole, and 50 ml of tetrahydrofuran was added a mixture of 0.27 g of N-methylhydroxylamine hydrochloride, 0.3 g of triethylamine, and 5 ml of N,N-dimethylformamide and the resultant mixture was stirred overnight at room temperature. Then, insoluble matters were filtered off and the filtrate thus formed was concentrated under reduced pressure. To the residue thus formed was added 100 ml of ethyl acetate and the mixture was washed with water, washed with a dilute aqueous solution of sodium hydrogencarbonate, and water, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. To the residue thus obtained was added ethyl acetate, then insoluble materials were filtered off and the filtrate formed was concentrated. The residue thus obtained was

recrystallized from a mixture of toluene and n-hexane to provide 0.18 g of 2-[[5-[[3-(4-acetyl-3-hydroxy-2-propylphenoxy)propyl]thio]-1,3,4-thiadiazol-2-yl]thio]-N-hydroxy-N-methylacetamide.

Melting point: 97 to 99°C

Elemental analysis for $C_{19}H_{25}N_3O_5S_3$:

	N
Calculated:	8.91%
Found:	9.06%

Example 52

(Tablet)

Compound of Ex. 21	30 mg
Lactose	104 mg
Corn starch	57 mg
Hydroxypropyl cellulose	4 mg
Calcium carboxymethyl cellulose	4 mg
Magnesium stearate	1 mg
total	200 mg

After uniformly mixing 30 g of compound of Ex. 21, 104 g of lactose and 57 g of corn starch, 40 ml of a 10%(w/w) aqueous solution of hydroxypropyl cellulose was added to the mixture and the resultant mixture was granulated by a wet granulation method. The granules thus obtained were mixed with 4 g of calcium carboxymethyl cellulose and 1 g of magnesium stearate and the mixture was press-tableted into tablets (200 mg per tablet).

Example 53

(Capsule)

Compound of Ex. 21	30 mg
Crystalline cellulose	40 mg
Crystalline lactose	129 mg
Magnesium stearate	1 mg
total	200 mg

The above components each in an amount 1000 times the foregoing amount were mixed and then filled into gelatin capsules to provide capsules (200 mg per capsule).

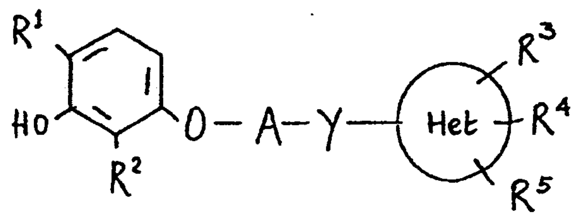
Example 54

(Inhalation)

After dissolving 0.1 g of compound of Ex. 21 in about 90 ml of a mixture of ethanol, propylene glycol and purified water (30:10:60 in weight ratio), the volume of the solution was adjusted to 100ml using the aforesaid mixture and 10 ml aliquots of the solution were filled into respective containers followed by sealing to provide an inhalation.

CLAIMS :

1. A heterocyclic compound of formula (I), or a salt thereof :



(I)

wherein R^1 represents a C_1 to C_6 acyl group; R^2 represents a C_1 to C_6 alkyl group; A represents a C_1 to C_6 alkylene group which may be hydroxy-substituted; Y represents an oxygen or sulfur atom or a carbonylimino or iminocarbonyl group; Het represents a 5- or 6-membered heterocyclic ring which contains 1 to 3 hetero atoms selected from oxygen, sulfur and nitrogen, is bonded directly to Y, and may be fused with a benzene ring; and R^3, R^4, and R^5, each of which may be present or absent, are the same or different and selected from C_1 to C_6 alkyl groups, groups of formula $-A^1-R^6$ [wherein A^1 represents a C_1 to C_6 alkylene group and R^6 represents a hydroxy, mercapto, carboxy, or (C_1 to C_6 alkoxy) carbonyl group], hydroxy and mercapto groups, C_1 to C_6 alkoxy groups, C_1 to C_6 alkylthio groups, groups of formula $-Y^1-A^2-R^7$ [wherein Y^1 represents an oxygen or sulfur atom, A^2 represents a C_1 to C_6 alkylene group, and R^7 represents a carboxy group, a (C_1 to C_6 alkoxy) carbonyl group, a hydroxyaminocarbonyl group, a mono- or di-(C_1 to C_6 alkyl) aminocarbonyl group, or an N-(C_1 to C_6 alkyl)-hydroxyaminocarbonyl group], oxo, thioxo and amino groups, groups of formula $-NH-R^8$ [wherein R^8 represents a carboxy (C_1 to C_6 alkyl) group or a (C_1 to C_6 alkoxy)carbonyl (C_1 to C_6 alkyl) group], groups of formula $-NH-CO-R^9$ [wherein R^9 represents a carboxy (C_1 to C_6 alkyl) group, a (C_1 to C_6 alkoxy) carbonyl (C_1 to C_6 alkyl) group, a (C_1 to C_6 alkoxy)phenyl (C_1 to C_6 alkoxy)carbonyl (C_1 to C_6 alkyl) group, a carboxy group or a (C_1 to C_6 alkoxy)carbonyl group], a carboxy group, and groups of formula $-CO-R^{10}$ [wherein R^{10} represents a C_1 to C_6 alkoxy group].

2. A compound according to claim 1 wherein Y is a sulfur atom or a carbonylimino group and R^3, R^4, and R^5, each of which may be present or absent, are the same or different and selected from groups of formula $-A^1-OH$, hydroxy, mercapto, and C_1 to C_6alkylthio groups, groups of formula $-Y^1-A^2-R^7$ [wherein Y^1 is a sulfur atom, A^2 is a C_1 to C_6 alkylene group, and R^7 is a carboxy group, a (C_1 to C_6 alkoxy)carbonyl group, or an N-(C_1 to C_6 alkyl)-hydroxyaminocarbonyl group], oxo, thioxo, and amino groups, groups of formula $-NH-R^8$, groups of formula $-NH-CO-R^9$, a carboxy group, and groups of formula $-CO-R^{10}$.

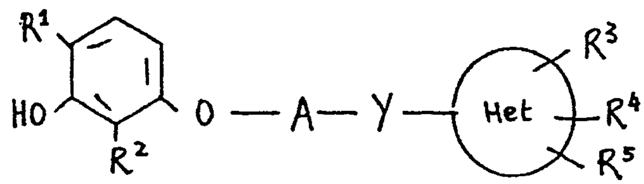
3. A compound according to claim 1 or 2 wherein R^1 is an acetyl group, R^2 is a propyl group, A is an alkylene group having 1 to 5 carbon atoms, Y is a sulfur atom, Het is a 1,3,4-thiadiazole ring, and R^3, R^4, and R^5, each of which may be present or absent, are the same or different and selected from hydroxy and mercapto groups, groups of formula $-Y^1-A^2-R^7$ [wherein Y^1 is a sulfur atom, A^2 is a C_1 to C_6 alkylene group, and R^7 is a carboxy group, (C_1 to C_6 alkoxy)carbonyl group, or an N-(C_1 to C_6 alkyl)-hydroxyaminocarbonyl group], an amino group, and groups of formula $NH-CO-R^9$.

4. A compound according to claim 1 or 2 wherein R^1 is an acetyl group; R^2 is a propyl group, A is an alkylene group having 1 to 5 carbon atoms; Y is a sulfur atom; Het is a pyrimidine ring; and R^3, R^4, and R^5, each of which may be present or absent, are the same or different and selected from hydroxy, mercapto, C_1 to C_6 alkythio, amino, and carboxy groups, and groups of formula $-COR^{10}$.

5. A compound according to claim 1 which is [[5-[[3-(4-acetyl-3-hydroxy-2-propylphenoxy)-propyl]thio]-1,3,4-thiadiazol-2-yl]thio]acetic acid or a salt thereof;

3-[[5-[[3-(4-acetyl-3-hydroxy-2-propylphenoxy)propyl]thio]-1,3,4-thiadiazol-2-yl]amino]-3-oxopropionic acid or a salt thereof;
4-[[5-[[3-(4-acetyl-3-hydroxy-2-propylphenoxy)propyl]thio]-1,3,4-thiadiazol-2-yl]thio]butyric acid or a salt thereof;
5-[[5-[[3-(4-acetyl-3-hydroxy-2-propylphenoxy)propyl]thio]-1,3,4-thiadiazol-2-yl]thio]valeric acid or a salt thereof;
2-[[5-[[3-(4-acetyl-3-hydroxy-2-propylphenoxy)propyl]thio]-1,3,4-thiadiazol-2-yl]thio]-N-hydroxy-N-methylacetamide or a salt thereof; or
6-[[-3-(4-acetyl-3-hydroxy-2-propylphenoxy)-propyl]thio]-2-methylthio-4-pyrimidinecarboxylic acid or a salt thereof.

6. A process of producing a compound of formula (I)

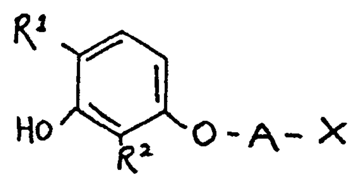


(I)

wherein R^1 represents a C_1 to C_6 acyl group; R^2 represents a C_1 to C_6 alkyl group; A represents a C_1 to C_6 alkylene group which may be hydroxy-substituted; Y represents an oxygen or sulfur atom or a carbonylimino or iminocarbonyl group; Het represents a 5- or 6-membered heterocyclic ring which contains 1 to 3 hetero atoms selected from oxygen, sulfur and nitrogen, is bonded directly to Y, and may be fused with a benzene ring; and R^3, R^4, and R^5, each of which may be present or absent, are the same or different and selected from C_1 to C_6 alkyl groups, groups of formula $-A^1-R^6$ [wherein A^1 represents a C_1 to C_6 alkylene group and R^6 represents a hydroxy, mercapto, carboxy, or (C_1 to C_6 alkoxy) carbonyl group], hydroxy and mercapto groups, C_1 to C_6 alkoxy groups, C_1 to C_6 alkylthio groups, groups of formula $-Y^1-A^2-R^7$ [wherein Y^1 represents an oxygen or sulfur atom, A^2 represents a C_1 to C_6 alkylene group, and R^7 represents a carboxy group, a (C_1 to C_6 alkoxy) carbonyl group, a hydroxyaminocarbonyl group, a mono- or di-(C_1 to C_6 alkyl) aminocarbonyl group, or an N-($C_1$to C_6 alkyl)-hydroxyaminocarbonyl group], oxo, thioxo and amino groups, groups of formula $-NH-R^8$

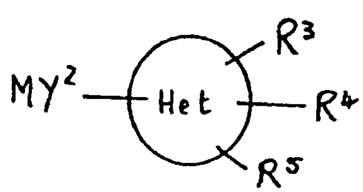
[wherein R^8 represents a carboxy (C_1 to C_6 alkyl) group or a (C_1 to C_6 alkoxy)carbonyl (C_1 to C_6 alkyl) group], groups of formula -NH-CO-R^9 [wherein R^9 represents a carboxy (C_1 to C_6 alkyl) group, a (C_1 to C_6 alkoxy) carbonyl (C_1 to C_6 alkyl) group, a (C_1 to C_6 alkoxy)phenyl (C_1 to C_6 alkoxy)carbonyl (C_1 to C_6 alkyl) group, a carboxy group or a (C_1 to C_6 alkoxy)carbonyl group], a carboxy group, and groups of formula -CO-R^{10} [wherein R^{10} represents a C_1 to C_6 alkoxy group]
which comprises either :

(a) reacting halogen compound of formula (II)



(II)

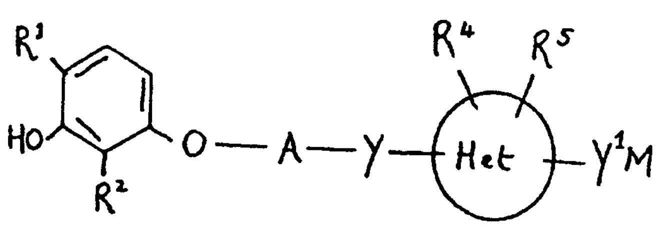
(wherein R^1, R^2 and A are as defined above and X represents halogen) and hydroxy- or mercapto-compound of formula (III)



(III)

or alkali metal-substituted compound thereof (wherein Het , R^3, R^4 and R^5 are as defined above, M represents hydrogen or alkali metal, and Y^2 represents an oxygen or sulfur atom); or

(b) reacting hydroxy- or mercapto-compound of formula (VIII)



(VIII)

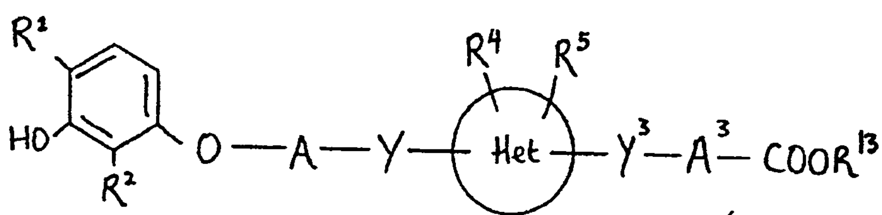
or alkali metal-substituted compound thereof (wherein R^1, R^2, A, Y, Het , R^4, R^5, Y^1 and M are as defined above) and halogen compound

of formula (IX)

$$X\text{-}A^2\text{-}R^7 \qquad \text{(IX)}$$

(wherein X, A^2 and R^7 are as defined above); or

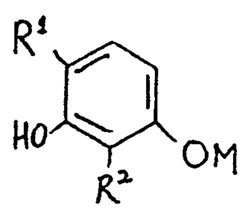
(c) hydrolizing ester compound of formula (Ii)



(Ii)

[wherein R^1, R^2, A, Y, Het , R^4 and R^5 are as defined above and Y^3 represents a single bond, an oxygen or sulfur atom or an imino group (-NH-); A^3 represents a single bond or a C_1 to C_6 alkylene group or when Y^3 is imino, may instead be a carbonyl or carbonyl (C_1 to C_6 alkylene) group; and R^{13} represents C_1 to C_6 alkyl group or a (C_1 to C_6 alkoxy) phenyl (C_1 to C_6 alkyl) group]; or

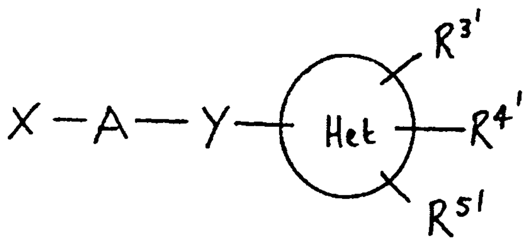
(d) reacting dihydroxybenzene derivative of formula (XII)



(XII)

or alkali metal-substituted compound thereof (wherein R^1, R^2 and M

are as defined ab[illegible]and halogen compound of formula (XIII)

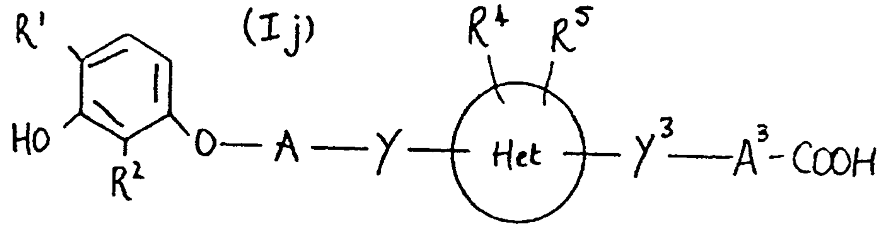


(XIII)

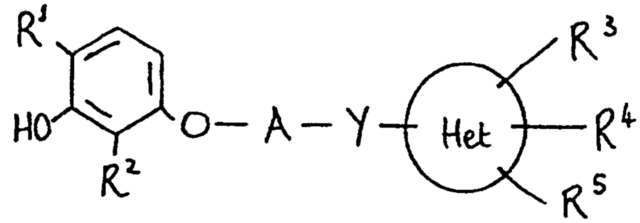
wherein X, A, Y and Het are as defined above and $R^{3'}$, $R^{4'}$ and $R^{5'}$, which may be present or absent, are the same or different and selected from C_1 to C_6 alkyl groups, groups of formula $-A^1-R^{6'}$ [wherein A^1 is as defined above and $R^{6'}$ represents a (C_1 to C_6 alkoxy)carbonyl group], a hydroxyl group, C_1 to C_6 alkoxy groups, C_1 to C_6 alkylthio groups, groups of formula $-Y^1-A^2-R^{7'}$ [wherein Y^1 and A^2 are as defined above and R^7 represents a (C_1 to C_6 alkoxy)carbonyl group, a hydroxyaminocarbonyl group, a mono- or di-(C_1 to C_6 alkyl) amino-carbonyl group or N-(C_1 to C_6 alkyl)-hydroxyaminocarbonyl group], an oxo group (=O=), an amino group, groups of formula $-NH-R^{8'}$ [wherein $R^{8'}$ represents a (C_1 to C_6 alkoxy)carbonyl (C_1 to C_6 alkyl) group], groups of formula $-NH-CO-R^{9'}$ [wherein $R^{9'}$ represents a (C_1 to C_6 alkoxy)carbonyl (C_1 to C_6 alkyl) group, a (C_1 to C_6 alkoxy)phenyl (C_1 to C_6 alkoxy)carbonyl (C_1 to C_6 alkyl) group or a (C_1 to C_6 alkoxy)carbonyl group], and groups of formula $-CO-R^{10}$ [wherein R^{10} is as defined above]; or

[e] esterifying compound of formula (Ij) below with alcohol $R^{13}OH$ or reactive derivative thereof (wherein R^{13} is as defined above).

(Ij)



7. A process of producing a compound of formula I :

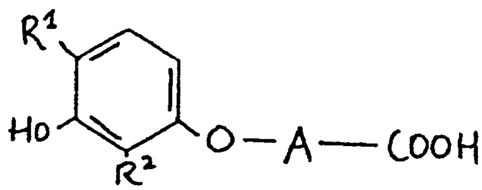


(I)

wherein R^1 represents a C_1 to C_6 acyl group; R^2 represents a C_1 to C_6 alkyl group; A represents a C_1 to C_6 alkylene group may be hydroxy-substituted: Y represents an oxygen or sulfur atom or a carbonylimino or iminocarbonyl group; Het represents a 5- or 6-membered heterocyclic ring which contains 1 to 3 hetero atoms selected from oxygen, sulfur and nitrogen, is bonded directly to Y, and may be fused with a benzene ring; and R^3, R^4, and R^5, each of which may be present or absent, are the same or different and selected from C_1 to C_6 alkyl groups, groups of formula $-A^1-R^6$ [wherein A^1 represents a C_1 to C_6 alkylene group and R^6 represents a hydroxy, mercapto, carboxy, or (C_1 to C_6 alkoxy) carbonyl group], hydroxy and mercapto groups, C_1 to C_6 alkoxy groups, C_1 to C_6 alkylthio groups, groups of formula $-Y^1-A^2-R^7$ [wherein Y^1 represents an oxygen or sulfur atom, A^2 represents a C_1 to C_6 alkylene group, and R^7 represents a carboxy group, a (C_1 to C_6 alkoxy) carbonyl group, a hydroxyaminocarbonyl group, a mono- or di-(C_1 to C_6 alkyl) aminocarbonyl group, or an N-($C_1$to C_6 alkyl)-hydroxyaminocarbonyl group], oxo, thioxo and amino groups, groups of formula $-NH-R^8$ [wherein R^8 represents a carboxy (C_1 to C_6 alkyl) group or a (C_1 to C_6 alkoxy)carbonyl (C_1 to C_6 alkyl) group], groups of formula $-NH-CO-R^9$ [wherein R^9 represents a carboxy (C_1 to C_6 alkyl) group, a (C_1 to C_6 alkoxy) carbonyl (C_1 to C_6 alkyl) group, a (C_1 to C_6 alkoxy)phenyl (C_1 to C_6 alkoxy)carbonyl (C_1 to C_6 alkyl) group, a carboxy group or a (C_1 to C_6 alkoxy)carbonyl group], a carboxy

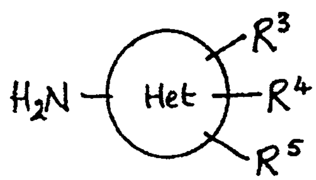
group, and groups of formula $-CO-R^{10}$ [wherein R^{10} represents a C_1 to C_6 alkoxy group]
which comprises either :

(i) reacting carboxylic acid (IV)



(IV)

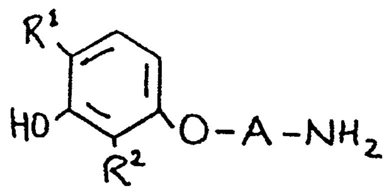
or reactive derivative thereof (wherein R^1, R^2 and A are as defined above) with amino compound (V)



(V)

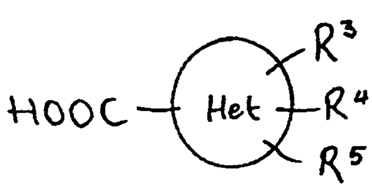
(wherein Het , R^3, R^4 and R^5 are as defined above); or

(ii) reacting amine (VI)



(VI)

(wherein R^1, R^2 and A are as defined above) with carboxylic acid (VII)

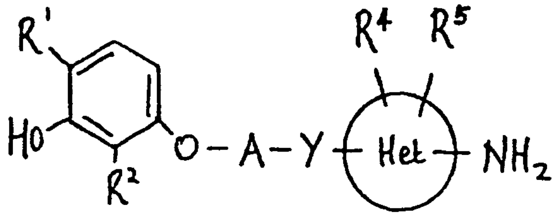


(VII)

or reactive derivative thereof (wherein Het , R^3, R^4 and R^5 are as

defined above); or

(iii) reacting amino compound (Ie)



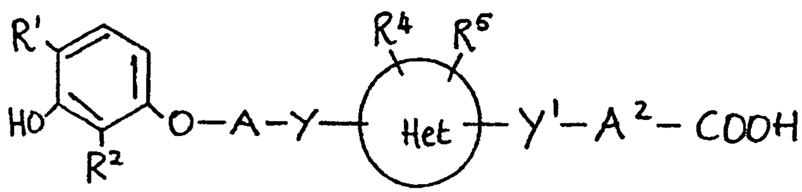
(Ie)

(wherein R^1, R^2, A, Y, (Het), R^4 and R^5 are as defined above) with carboxylic acid (X)

$$HOOC-R^9 \qquad (X)$$

or reactive derivative thereof (wherein R^9 is as defined above); or

(iv) reacting carboxylic acid (Ig)



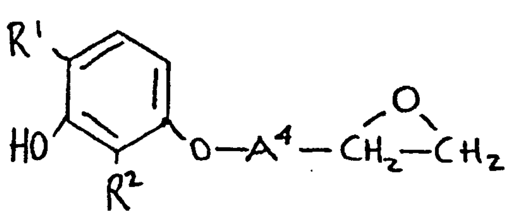
(Ig)

or reactive derivative thereof (wherein R^1, R^2, A, Y, (Het), R^4, R^5, Y^1 and A^2 are as defined above) with amine (XI)

$$HN\genfrac{}{}{0pt}{}{R^{11}}{R^{12}} \qquad (XI)$$

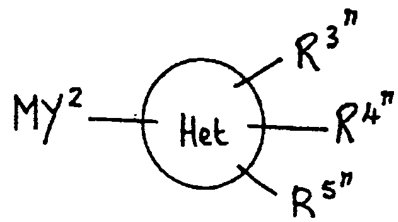
(wherein R^{11} represents a hydrogen atom or a C_1 to C_6 alkyl group and R^{12} represents a C_1 to C_6 alkyl group or a hydroxyl group); or

(v) reacting epoxy compound (XIV)



(XIV)

(wherein R^1 and R^2 are as defined above and A^4 represents a single bond or a C_1 to C_6 alkylene group) with hydroxy- or mercapto-compound (XV)



(XV)

or alkali metal substituted compound thereof [wherein M, Y^2 and (Het) are as defined above and $R^{3''}$, $R^{4''}$ and $R^{5''}$, each of which may be present or absent, are the same or different and selected from C_1 to C_6 alkyl groups, a hydroxyl group, groups of formula $-A^1-R^{6''}$ (wherein A^1 is as defined above and $R^{6''}$ represents a hydroxyl,carboxy or (C_1 to C_6 alkoxy)carbonyl group), C_1 to C_6 alkoxy groups, C_1 to C_6 alkylthio groups, groups of formula $-Y^1-A^2-R^7$ (wherein Y^1, A^2 and R^7 are as defined above) an oxo group, an amino group, groups of formula $-NH-R^8$ (wherein R^8 is as defined above), groups of formula $-NH-CO-R^9$ (wherein R^9 is as defined above), a carboxy group, and groups of formula $-CO-R^{10}$ [wherein R^{10} is as defined above].

8. A process according to claim 6 or 7 including the step of converting the product to or from salt form.

9. A pharmaceutical composition containing a compound according to any of claims 1 to 5.

10. A composition according to claim 9 capable of antagonizing the actions of SRS-A or inhibiting the production and release of SRS-A and containing [[5-[[3-(4-acetyl-3-hydroxy-2-propylphenoxy)-propyl]thio-1,3,4-thiadiazol-2-yl]thio]-acetic acid or a pharmaceutically acceptable salt thereof.

11. A process according to claim 6 or 7 or 8 wherein compound (II) is 4-(3-halogenopropoxy)-2-hydroxy-3-propylacetophenone and compound (III) is[(5-mercapto-1,3,4,-thiadiazol-2-yl)thio]acetic acid; or compound (VIII) is 2-hydroxy-4-[[3-(5-mercapto-1,3,4-thiadiazol-2-yl)thio]propoxy]-3-propylacetophenone and compound (IX) is halogenaocetate; or ester (Ii) is (C_1 to C_6 alkyl)- or (C_1 to C_6 alkoxy)phenyl (C_1 to C_6 alkyl)-[[5-[[3-(4-acetyl-3-hydroxy-2-propylphenoxy)propyl]thio]-1,3,4,-thiadiazol-2-yl]-thio]-acetate.

European Patent Office

EUROPEAN SEARCH REPORT

1 81779 Application number

EP 85308227.9

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int Cl 4)
A	EP - A1 - 0 084 673 (BASF AKTIENGESELLSCHAFT) * Claims 1,3 * --	1,6	C 07 D 285/12 C 07 D 277/16 C 07 D 277/74 C 07 D 239/58 C 07 D 249/12 A 61 K 31/41 A 61 K 31/425 A 61 K 31/505
A	EP - A1 - 0 067 685 (AMERICAN HOME PRODUCTS CORPORATION) * Claims 1,10 * --	1,6	
P,A	GB - A - 2 139 623 (BRISTOL-MYERS COMPANY) * Claims 1,38 * --	1,6	
A	US - A - 4 382 142 (TAKATORI et al.) * Abstract * --	1	TECHNICAL FIELDS SEARCHED (Int. Cl.4)
A	US - A - 4 411 905 (ALBRECHT et al.) * Abstract * ----	1	C 07 D 285/00 C 07 D 277/00 C 07 D 239/00 C 07 D 249/00

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
VIENNA	19-02-1986	BRUS

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
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